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(54) Title: HIV ENVELOPE POLYPEPTIDES AND VACCINE

(57) Abstract

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Oligonucleotide sequences encoding gp120 polypeptides from breakthrough isolates of vaccine trials using MN-rgp120 and the encoded gp120 polypeptides are provided. Use of the gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g., MN-rgp120) that the vaccine does not confer protection against those strains. Antibodies induced by the polypeptides are also provided.

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HIV ENVELOPE POLYPEPTIDES AND VACCINE

BACKGROUND OF THE INVENTION

5 Field of the Invention

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This invention relates to HIV envelope polypeptides.

Description of the Related Art

10 Acquired immunodeficiency syndrome (AIDS) is
caused by a retrovirus identified as the human
immunodeficiency virus (HIV). There have been intense
efforts to develop a vaccine that induces a protective
immune response based on induction of antibodies or
15 cellular responses. Recent efforts have used subunit
vaccines where an HIV protein, rather than attenuated
or killed virus, is used as the immunogen in the
vaccine for safety reasons. Subunit vaccines generally
include gp120, the portion of the HIV envelope protein
which is on the surface of the virus.

The HIV envelope protein has been extensively described, and the amino acid and nucleic acid sequences encoding HIV envelope from a number of HIV strains are known (Myers, G. et al., 1992. Human Retroviruses and AIDS. A compilation and analysis of nucleic acid and amino acid sequences. Los Alamos National Laboratory, Los Alamos, New Mexico). The HIV envelope protein is a glycoprotein of about 160 kd (gp160) which is anchored in the membrane bilayer at its carboxyl terminal region. The N-terminal segment, gp120, protrudes into the aqueous environment surrounding the virion and the C-terminal segment, gp41, spans the membrane. Via a host-cell mediated process, gp160 is cleaved to form gp120 and the integral membrane protein gp41. As there is no covalent attachment between gp120 and gp41, free gp120 is sometimes released from the surface of virions and

infected cells.

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The gp120 molecule consists of a polypeptide core of 60,000 daltons which is extensively modified by N-linked glycosylation to increase the apparent molecular weight of the molecule to 120,000 daltons. The amino acid sequence of gp120 contains five relatively conserved domains interspersed with five hypervariable domains. The positions of the 18 cysteine residues in the gp120 primary sequence, and the positions of 13 of the approximately 24 N-linked glycosylation sites in the gp120 sequence are common to all gp120 sequences. The hypervariable domains contain extensive amino acid substitutions, insertions and deletions. Sequence variations in these domains result in up to 30% overall sequence variability between gp120 molecules from the various viral isolates. Despite this variation, all gp120 sequences preserve the ability of the virus to bind to the viral receptor CD4 and to interact with gp41 to induce fusion of the viral and host cell membranes. 20

gp120 has been the object of intensive investigation as a vaccine candidate for subunit vaccines, as the viral protein which is most likely to be accessible to immune attack. At present, clinical trials using gp120 MN strain are underway. However, to date no human vaccine trial has been of sufficient size to confirm or refute vaccine efficacy.

The development of candidate HIV-1 vaccines is burdened by the lack of in vivo or in vitro models of HIV-1 infection that accurately approximate the conditions of natural infection in humans. Several candidate HIV-1 vaccines [Berman et al.; J. Virol. 7:4464-9 (1992); Haigwood et al.; J. Virol. 66:172-82 (1992); Salmon-Ceron et al.; AIDS Res. and Human Retroviruses 11:1479-86 (1995)] have been described that elicit broadly cross-reactive antibodies able to

neutralize a variety of diverse HIV-1 isolates in vitro. However, the relevance of in vitro assays to protective immunity in vivo is uncertain. Although several vaccines have provided chimpanzees with protection from challenge by homologous and heterologous strains of HIV-1, protection has not always correlated with in vitro neutralization assays carried out in T cell lines, or in lectin- and cytokine-activated peripheral blood mononuclear cells (PBMCs) [Berman et al.; Nature 345:622-5 (1990); Bruck et al.; Vaccine 12(12):1141-8 (1994); El-Amad et al.; AIDS 9:1313-22 (1995); Girard et al.; J. Virol. 69:6239-48 (1995); and Fulz et al; Science 256:1687-1690 (1992)]. While successful protection of chimpanzees is encouraging and has historically proved to be a reliable indicator of vaccine efficacy, the conditions of infection in all experimental models of HIV-1 infection differ significantly from natural infection in humans.

Experimental HIV-1 infection in vivo and in vitro 20 both suffer from the limitation that the in vitro amplification of HIV-1, which is required to prepare virus stocks for in vitro or in vivo infectivity experiments, imposes a genetic selection that results in a spectrum of virus quasi-species that differ from 25 the spectrum of variants present in the clinical specimens used to establish the culture [Kusumi et al., $extcolor{black}{ ilde{J}}$, $extcolor{black}{ ilde{Virol}}$. $extcolor{black}{ ilde{G}}$ 66:875 (1992); Meyerhans et al.; $extcolor{black}{ ilde{C}}$ 58:901-10 (1989)]. Because of these uncertainties, and even greater uncertainties related to the amount of virus transmitted, the site and cell type involved in initial replication, and the kinetics of virus dissemination, the ability of currently available in vitro or in vivo assays to reliably predict vaccine efficacy is questionable.

One of the candidate HIV-1 vaccines that have

entered human clinical trials is recombinant gp120 prepared in Chinese hamster ovary (CHO) cells from the MN strain of HIV-1 (MN-rgp120) (Berman et al.; J. Virol. 7:4464-9 (1992)). To date, approximately 499 adults have participated in Phase 1 and 2 immunogenicity and safety trials of this vaccine. The data collected thus far suggest that MN-rgp120 is safe, immunogenic, and elicits high titers of neutralizing antibodies in greater than 95% of individuals immunized according to a 0, 1, and 6 month immunization schedule [Belshe et al.; JAMA 272(6):475-80 (1994); McElrath; Seminars in Cancer Biol. 6:1-11 (1995)]. However, during the course of these trials, nine vaccinees who received MN-rgp120 have become infected with HIV-1 through high risk behavior. Small trials, such as these, in populations with low rates of infection and minimally sized placebo control groups do not have sufficient statistical power to confirm or refute vaccine efficacy.

20 However, effective vaccines based on gp120 or another HIV protein for protection against additional strains of HIV are still being sought to prevent the spread of this disease.

25 Description of the Background Art

Recombinant subunit vaccines are described in Berman et al., PCT/US91/02250 (published as number WO91/15238 on 17 October 1991). See also, e.g. Hu et al., Nature 328:721-724 (1987) (vaccinia virus-HIV envelope recombinant vaccine); Arthur et al., J. Virol. 63(12): 5046-5053 (1989) (purified gp120); and Berman et al., Proc. Natl. Acad. Sci. USA 85:5200-5204 (1988) (recombinant envelope glycoprotein gp120).

Numerous sequences for gp120 are known. The sequence of gp120 from the IIIB substrain of $HIV-1_{LAI}$

referred to herein is that determined by Muesing et al., "Nucleic acid structure and expression of the human AIDS/lymphadenopathy retrovirus, Nature 313:450-458 (1985). The sequences of gp120 from the NY-5, Jrcsf, 26, Z321, and HXB2 strains of HIV-1 are listed by Myers et al., "Human Retroviruses and AIDS; A compilation and analysis of nucleic acid and amino acid sequences," Los Alamos National Laboratory, Los Alamos, New Mexico (1992). The sequence of the Thai isolate A244 is provided by McCutchan et al., "Genetic Variants 10 of HIV-1 in Thailand, " AIDS Res. and Human Retroviruses 8:1887-1895 (1992). The MN₁₉₈₄ clone is described by Gurgo et al., "Envelope sequences of two new United States HIV-1 isolates, " Virol. 164: 531-536 (1988). As used herein, MN, MN-rgp120, the MN clone or isolate 15 refers to MN_{GNE} . The MN_{GNE} amino acid sequence is Sequence ID No. 29.

Each of the above-described references is incorporated herein by reference in its entirety.

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Summary of the Invention

Oligonucleotide sequences encoding gp120
polypeptides from breakthrough isolates of vaccine
trials using MN-rgp120 and the encoded gp120
polypeptides are provided. Use of the gp120
polypeptides from one or more of the isolates in a
subunit vaccine, usually together with MN-rgp120, can
provide protection against HIV strains that are
sufficiently different from the vaccine strain (e.g.;
MN-rgp120) that the vaccine does not confer protection
against those strains. Antibodies induced by the
polypeptides are also provided.

Brief Description of the Drawings

Figure 1 illustrates the kinetics of antibody response to MN-rgp120 in vaccinees infected with HIV-1.

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Sera were collected at the time points indicated and assayed for antibodies reactive with MN-rgp120 (open circles) or a synthetic peptide derived from the V3 domain of MN-rgp120 (closed circles). Arrows indicate dates of injection. Plus sign indicates the first time HIV-1 infection was detected. Shaded area indicates data collected after HIV-1 infection. Data from vaccinee C6 is shown in panel A; C8 in panel B; C7. panel C; C11, panel D; C10, panel E; C17, panel F; and C15, panel G.

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Figure 2 illustrates the kinetics of CD4 blocking antibody response in vaccinees infected with HIV-1. Sera were collected at the time points indicated and assayed for antibodies able to block the binding of [125I]-labeled MN-rgp120 to cell surface CD4. Arrows indicate dates of injection. Plus sign indicates the first time HIV-1 infection was detected. Shaded area indicates data collected after HIV-1 infection. Data from vaccinee C6 is shown in panel A; C8 in panel B; C7, panel C; C11, panel D; C10, panel E; C17, panel F; and C15, panel G.

Figure 3 illustrated predicted amino acid sequences of envelope glycoproteins (gp120) from breakthrough viruses. Proviral DNA sequences were amplified by PCR from PBMCs and cloned into the PRK5 expression plasmid. Two clones from each infected vaccinee were sequenced from double stranded plasmid Sequence numbering is with reference to the initiator methionine residue of gp120. For the purpose of comparison, the sequences shown begin at amino acid 12 of the mature, fully processed, envelope glycoproteins (corresponding to position 41 of the gp120 open reading frame). Shaded areas indicate sequences at neutralizing epitopes, dark boxes indicate 35 polymorphisms thought to be important for the binding of virus neutralizing MAbs reactive with MN-rgp120.

Conserved (C) regions and variable (V) regions are indicated above the sequences. Boxes indicate sequence homologies and polymorphisms.

Figure 4 illustrates immunoprecipitation of recombinant gp120 prepared from breakthrough viruses. Recombinant gp120s from the seven breakthrough viruses were prepared by transient transfection of 293s cells. Cells were metabolically labeled with "S methionine and growth conditioned cell culture supernatants were immunoprecipitated with polyclonal antisera to MN-rgp120. Immunoprecipitates were resolved by SDS-PAGE and visualized by autoradiography. C8 lanes a and b correspond to clones C8.3 and C8.6; C6 lanes a and b correspond to clones C6.1 and C6.5; C7 lanes a and b correspond to clones C7.2 and C7.10; C17 lanes a and b correspond to C17.1 and C17.3; C11 lanes a and b correspond to clones C11.5 and C11.7; C10 lanes a and b correspond to clones C10.5 and C10.7; C15 lanes a and b correspond to clones C15.2 and C15.3.

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Figure 5 illustrates binding of monoclonal antibodies to recombinant gp120 from breakthrough viruses. Growth-conditioned cell culture supernatants were collected from 293s cells transiently transfected with plasmids directing the expression of breakthrough virus envelope glycoproteins. The relative rgp120 concentrations were determined by ELISA using MAb 5B6 specific for the HSV-1 glycoprotein D flag epitope at the amino terminus of all of the rgp120 variants described herein. The resulting rgp120 preparations were captured onto wells of microtiter plates coated with a polyclonal antibody specific for a conserved sequence in the C-terminus of gp120. The binding of virus neutralizing monoclonal antibodies reactive with gp120 was determined by ELISA. A, binding by MAb (5B6) specific for the HSV-1 glycoprotein D flag epitope; B, binding by MAb (1034) against the V3 domain of

MN-rgp120; C binding by MAb (50.1) raised against a synthetic peptide corresponding to the V3 domain of MN-rgp120; D, binding by a human MAb (15e) known to block the binding of gp120 to CD4.

Figure 6 depicts the mature envelope glycoprotein (gp120) from the MN clone of the MN strain of HIV-1 (SEQ. ID. NO. 29). Hypervariable domains are indicated in bold, and the V and C regions are indicated (according to Modrow et al., J. Virology 61(2):570 (1987). Potential glycosylation sites are marked with a (*).

Detailed Description of the Invention

The present invention provides gp120 polypeptides

from breakthrough isolates of HIV vaccine trials.

Novel oligonucleotide sequences encoding gp120 from

breakthrough isolates which can be used to express

gp120 are also provided. Use of gp120 polypeptides

from one or more of the isolates in a subunit vaccine,

usually together with MN-rgp120, can provide protection

against HIV strains that are sufficiently different

from the vaccine strain (e.g.; MN-rgp120) that the

vaccine does not confer protection against those

strains.

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In one embodiment, the vaccine is based on the use of the MN-rgp120 polypeptide (Sequence ID No. 29) and gp120 polypeptides from MN-like viruses that include neutralizing epitopes that are not present in the initial vaccine strain, and are sufficiently different from those of the vaccine strain, to have been able to cause HIV-1 infections in MN-rgp120 vaccinated individuals (i.e.; to result in breakthrough infections). Use of the initial vaccine strain empirically determines the viruses present in the population that contain additional neutralizing epitopes sufficiently different from those of the

vaccine strain to escape protection induced by the vaccine strain. Use of an initial representative gp120 polypeptide in a vaccine acts as a sieve so that viruses that are not effectively protected against by the vaccine strain breakthrough the vaccine, empirically resulting in determination of additional strains in a given geographic region that are not protected against by the initial vaccine strain. Use of gp120 from those breakthrough isolates complements the vaccine isolate by providing additional neutralizing epitopes not present in the initial vaccine strain, therefore creating a more complete vaccine that confers protection against multiple different virus strains in the region.

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Prior HIV-1 vaccine strategies were based on selection of appropriate candidate vaccine polypeptides based on homology alignment studies. However, since some of the neutralizing epitopes are conformationdependent and the location of all of these epitopes is not known, this approach necessarily cannot determine all of the neutralizing epitopes that should be included in a vaccine for a particular region. In contrast, the present approach uses a selected representative strain and empirically determines strains that are sufficiently different and therefore breakthrough the barrier of protection provided by the initial vaccination program. Those strains can be included in the vaccine to confer more complete protection from HIV strains in the region. addition, those strains can be used alone to confer protection against the breakthrough virus.

In another embodiment, the invention comprises a vaccine containing a first HIV gp120 polypeptide sequence and a breakthrough isolate HIV gp120 polypeptide sequence from a vaccinee vaccinated with a vaccine including the first HIV gp120 polypeptide

sequence, the HIV gp120 polypeptide sequences being in a suitable carrier. Fragments of one or both HIV gp120 polypeptide sequences can be substituted for one or both of the corresponding HIV gp120 polypeptide sequences.

Preferably, the first gp120 polypeptide sequence contains neutralizing epitopes found in one or more gp120 polypeptides present in isolates from the geographical region where the initial vaccine (i.e., the vaccine that gives rise to the breakthrough isolate) is administered. More preferably, the first gp120 polypeptide sequence contains at least one of the more common neutralizing epitopes for the region, and most preferably the first gp120 polypeptide sequence contains at least one of the three most common neutralizing epitopes.

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gp120 polypeptide sequences suitable for use as the first gp120 polypeptide sequence include gp120 MN, the Thai isolate A244 sequence (hereinafter "gp120 A244"), gp120 MN-GNE6 (Sequence ID No. 31; also known in the art as "gp120 GNE6"), and gp120 MN-GNE8 (Sequence ID No. 33; also known in the art as "gp120 GNE8"), and the like. gp120 MN, gp120 MN-GNE6, and gp120 MN-GNE8 are especially preferred for use as the first gp120 polypeptide sequence in initial vaccines for North America. gp120 A244 is especially preferred for use as the first gp120 polypeptide sequence in initial vaccines for North America. gp120 polypeptide sequence in initial vaccines for Thailand.

In a variation of this embodiment, the vaccine includes two different (i.e., first and second) gp120 polypeptide sequences, or fragments thereof, in combination with a breakthrough isolate HIV gp120 polypeptide sequence. The latter can be from a vaccinee vaccinated with either or both of the first and second HIV gp120 polypeptide sequences.

Exemplary vaccines include those containing

combinations of gp120 MN, gp120 A244, gp120 MN-GNE6 (Sequence ID No. 31), and gp120 MN-GNE8 (Sequence ID No. 33). Combinations of gp120 MN and gp120 A244 or gp120 MN-GNE8 (Sequence ID No. 33) with a breakthrough isolate HIV gp120 polypeptide sequence are especially preferred.

In vaccines containing gp120 MN, the breakthrough isolate HIV gp120 polypeptide sequence can be an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.

The term "subunit vaccine" is used herein, as in the art, to refer to a viral vaccine that does not contain virus, but rather contains one or more viral proteins or fragments of viral proteins. As used herein, the term "multivalent", means that the vaccine contains gp120 from at least two HIV isolates having different amino acid sequences.

The term "breakthrough isolate" or "breakthrough virus" is used herein, as in the art, to refer to a virus isolated from a vaccinee.

The terms "amino acid sequence", "polypeptide sequence", and "polypeptide" are used interchangeably herein as in the art, as are the terms "nucleic acid sequence", "nucleotide sequence", and "oligonucleotide".

Polypeptides from Breakthrough Isolates

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The gp120 polypeptides of this invention correspond to the amino acid sequences of seven breakthrough isolates which are illustrated below in Table 1. A polypeptide of this invention includes an HIV gp120 amino acid sequence illustrated in Table 1 (Sequence ID Nos. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27) and fragments thereof. The polypeptides of this invention can include fused

sequences from two or more HIV gp120 or gp160 amino acid sequences.

The polypeptide can also be joined to another viral protein, such as a flag epitope amino acid sequence. The term "flag epitope" is used herein, as in the art, to denote an amino acid sequence that includes an epitope recognized by a monoclonal antibody. Flag epitopes facilitate using single monoclonal antibody affinity purification of a 10 plurality of different recombinant proteins, each having the flag epitope recognized by the monoclonal antibody. Numerous amino acid sequences can function. as flag epitopes. The N-terminal sequences of Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (gD-1) is 15 conveniently used as the flag epitope and its use is described in detail in the examples. The flag epitope is conveniently fused to the N terminus of the HIV gp120 polypeptide sequence. Alternatively, however, monoclonal antibodies that recognize neutralizing 20 epitopes in the rgp120 sequences can be used to affinity purify the amino acid sequences, and a flag epitope can be omitted.

In addition, various signal sequences can be joined to a polypeptide of this invention. Although rgp120 is secreted to some extent in HIV cultures, the amount of the envelope glycoprotein released from (secreted by) the host cells varies widely from strain to strain. Various signal sequences can be introduced into the polypeptide by joining a nucleotide sequence encoding the signal sequence to the nucleotide sequence encoding the rgp120 to facilitate secretion of rgp120 from the cells. For example, Chiron HIV gp120 polypeptides include a signal sequence from tissue plasminogen activator (TPA) that provides good secretion of rgp120. Additional signal sequences are well known and include the N-terminal domain of murine

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leukemia virus surface protein gp70 described by Kayman et al., $J.\ Virol.\ 68:400-410\ (1984)$.

Table 1 illustrates the nucleotide and deduced amino acid sequences for two clones of each the seven breakthrough isolates of this invention. The clones are: C6.1; C6.5; C8.3; C8.6; C15.2; C15.3; C7.2; C7.10; C11.5; C11.7; C10.5; C10.7; C17.1; and C17.3. These sequences are SEQ. ID. NOs. 1-28, the first sequence number for each clone being the nucleotide sequence and the second being the amino acid sequence. The amino acid sequence for MN and the nucleotide and deduced amino acid sequences for MN-GNE6 and MN-GNE8 are illustrated in the sequence listing hereinafter. In the listing for MN-GNE6, a stop codon appears at amino acid residue position 51. This stop codon can be replaced with a codon encoding the corresponding amino acid from MN or MN-GNE8 or another isolate.

TABLE

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4000	ACT	AGC	TAT	AGG	TTG	AGA	AGT	TGT	AAC	ACC	TCA	GTC	ATT	543
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Thr		Tyr	Arg	Leu	Arg	Ser	Cys	Asn	Thr	Ser	Val	Ile	
45		170	000		CC1	220	175	N.CT		' :' .	CCA	180		582
	Thr	Glin	Ala	Cva	Pro	LVE	Val	Thr	Phe	Glu	Pro	Ile	Pro	
				185				1 .	190	1 1 11 1	1. 1 1 . "			
	ATA	CAT	TAT	TGT	ACC	CCG	GCT	GGT	TTT	GCG	ATT	CTG	AAG	621
50			Tyr	Cys	Thr	Pro	Ala	Gly			Ile	Leu	Lys	
	195	202	C 3 m	A B B		200	አስጥ	CCA	D C D	CGA.	CCA	TCC	D . D . D .	660
0 0	CVE	Ara	Acn	Tue	TVE	Pho	VU1	Clv	Thr	CIV	Pro	CVS	Lvs	000
	•		210					215			1.1.1		:220	
55	AAT	GTT	AGC	ACA	GTA	CAA	TGT	GCA	CAT	GGA	ATT	AAG	CCA	699
	Asn	Val	Ser	Thr	Val	Gln	Cys	Ala	His	Gly	Tle	Lys	Pro	
			:		225	ama			2.20	.230	N.C.C	 Combi	CCA	770
	GTA	GTG	TCA	ACT	CAA	CTG	CTG	TTA	AAI	GGC.	AGC Ser	LOU	Ala	130
60		235	ser	· · · · · · · · · · · · · · · · · · ·	ĢΙŊ	Leu	240	Leu	nail	Y		245		
,55	GAA	GAA	GAG	GTA	ATA	ATT	AGA	TCT	GCC	AAT	TTC	TCA	AAC	777
	Glu	Glu	Glu	Val	Ile	Ile	Arg	Ser	Ala	Asn	Phe	Ser	Asn	
				250			٠.		255			: P		

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AAT GCT AAA ATC ATA ATA GTA CAG TTG AGG GAA CCT GTA 815
     Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu Pro Val
                           265
     GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
      Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
                                                        285
                                   280
              275
      GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
      Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
                       290
      GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
      Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
                               305
      ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
      Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
                                        320
                  315
      GTT AAA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
       Val Lys Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
                            330
      GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
      Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
20
                                                        350
                                   345
              340
      ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
      Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
                                            360
                       355
      AAT ACA ACA AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
                                                    3.75
                               370
          365
      ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
Thr Glu Ser Asn Asn Asn Ser Thr Ile Thr Leu Pro
                                        385
                   380
      TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA ATA 1206
      Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile
                           395
      GGA AAA GCA ATG TAT GCC CCT CCC ACC AGA GGA GAA ATT 1245
      Gly Lys Ala Met Tyr Ala Pro Pro Thr Arg Gly Glu Ile
35 -
                                   410.
              405
      AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ATA AGA 1284
      Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Ile Arg
                       420
      GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
40
      Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
                               435
                                                     440
      AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
      Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
45
                                        450
      GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
      Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
                                                465
                           460
      455
      GGA GTA GCA CCC ACC AAG GCA AAG AGA GTG GTG CAG 1440
      Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
50
                                   475
               470
      AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
      Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
                                            490
                       485
      GGG TTC TTA GGA GCA TAA AGC TTC 1503
      Gly Phe Leu Gly Ala Xaa Ser Phe
                                500 501
           495
                                  CLONE C6.5
           GGG GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA 36
           Gly Val Pro Val Trp Lys Glu Ala Thr Thr Leu
                                                  . 10
                               5
       TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
       Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
                                     20
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CAT AAT GIT TGG GCC ACA CAT GCT TGT GTA CCC AGA GAC 114
     His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
      CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
      Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
          40
      GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
      Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
                                        60
      CAT GAG ANT ATA ATC AGT TTA TGG GAT CAA AGC CTA AAA 231
      His Glu Xaa Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
                            70
      CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
      Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
15
             80
                                   85
                                                        90
      TGC ACC AAT TGG AAG GAG AAT GAT ACT AAA ACT AAT AGT 309
Cys Thr Asn Trp Lys Glu Asn Asp Thr Lys Thr Asn Ser
                       95
                                            100
      AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
      Ser Ser Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
20
                             .. 110
      AGT AGT ACT ACA ACT AAT AGT AGT TGG GGA GAG ATA 387
Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
                  120
                                       125
      AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
25
      Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
                           1:35
      ACA GGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465...
      Thr Gly Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
30
              1.45
                                   150
      TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
      Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
                                          165
                   160
      ACT AGC TAT AGG TTG AGA AGT TGT AAC ACC TCA GTC ATT 543
35
      Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
         170
                               175
                                                   180
      ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
      Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
                                       190
                  185
      ATA CAT TAT TGT ACC CCG GCT GGT TTT GCG ATT CTG AAG 621
      Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
                                               205
      195
TGT AAA GAT AAA AAG TTC AAT GGA ACA GGA CCA TGC AAA 660
      Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
45
              210
                                   215
      AAT GTT AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG CCA 699
      Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro
                                           230
      GTA GTG TCA ACT CAA CTG CTG TTA AAT GGC AGC CTA GCA 738
50
      Val Val Ser Thr Gin Leu Leu Leu Asn Gly Ser Leu Ala
                               240
      GAA GAA GAG GTA ATA ATT AGA TOT GCC AAT TTC TCA AAC 777
      Glu Glu Glu Val Ile Ile Arg Ser Ala Asn Phe Ser Asn
55
      AAT GCT AAA ATC ATA ATA GTA CAG TTG AAG GAA CCT GTA 816
      Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu Pro Val
                           265
      GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
      Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
60
              275
                                   280
                                                        2.85
      GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
      Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
                                          295
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GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
     Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
                             305
     ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
     Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
                                     320
     GTT ATA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
     Val Ile Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
                                             335
                         330
     .325
    GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
    Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
340 345
     ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
     Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
                                         360
                     355
     AAT ACA ACG AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
     Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
                             370
     ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
         365
     Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
20
                                     385
                 380
     TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA 1206
     Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val-
                          395
     GGA AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA GAA ATT 1245
25
     Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile
                                 410
     AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ACA AGA 1284
     Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Thr Arg.
                     420
                                          425
     GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
     Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
                                                440
                              435
         430
     AGA CCG GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
     Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
                                      450
                 445
     GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
     Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
      455
     GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
      Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
             470
                                 475
      AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
      Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
                      485
      GGG TTC TTG GGA GCA TAA AGC TTC 1503
      Gly Phe Leu Gly Ala Xaa Ser Phe
          495
                                   CLONE C8.3
      G GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
       Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
                                               10
      TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
      Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
                                   20
      AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
      Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
      AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
60
      Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
                               45
        40
      TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
      Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
                                       60
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GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
      Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
                           70
      TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
      Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
               80
      ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
      Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
                       95
                                          100
      AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
      Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
                               110
                                                   115
      ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
      Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
                  120
                                       125
15
      GAT AAG GTG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
      Asp Lys Val Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
      130
                          135
                                               140
      GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
20
      Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
              145
                                  150
                                                       155
      ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505.
The Ser Cys Asn Thr Ser Val The Thr Gln Ala Cys Pro
                      160
                                           165
      AAG GTA TCC TTT GAG CTA ATT CCC ATA CAT TAT TGT GCC 544
25
      Lys Val Ser Phe Glu Leu Ile Pro Ile His Tyr Cys Ala
          170
                              175
      CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
     Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
3.0
                  185
      TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA GTA 622
      Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val
                          200
                                               205
      CAN TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
      Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
35
              210
                                   215
                                                       220
      CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
      Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
                      225
      ATT AGA TOT GAA AAT ATC ACA GAC AAT GOT AAA ACC ATA 739
40
      Ile Arg Sen Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
                             240
          235
      ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
      Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
45
                  250
      AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
      Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
                                               270
                          265
      CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
50
      Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
              275
                                  280
                                                       285
      GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
      Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
                      290
                                          295
55
      TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
      Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
                              305
      GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
      Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
                                       320
                  315
      TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
      Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
                          330
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TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA AAA CTG 1051
Cys Gly Glu Ph Phe Tyr Cys Asn Thr Thr Lys Leu
                                    345
      TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
      Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
 5
                                            360
      ACC GGG AAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
      Thr Gly Asn Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
                                                     375
          365
                                3.7.0
      TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
      Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
                                         385
                   380
      GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
      Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
                                                 400
                           395
      390
      AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA ACA AGA 1246
      Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg
                                    410
               405
      GAT GGT GGA AGT AAC ACC GGT GAC AAC AGG ACT GAG ACC 1285
      Asp Gly Gly Ser Asn Thr Gly Asp Asn Arg Thr Glu Thr
2.0
                                            425
                       420
      TTT AGA CCT GGA GGA GGT ATG AGG GAC AAT TGG AGA 1324
      Phe Arg Pro Gly Gly Asp Met Arg Asp Asn Trp Arg
                                435
          430
      AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
25
      Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
                                       450
      TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
      Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
                                                 465
                            460
3:0
      CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
      CTT GGG TTC TTG GGA GAT AA 1461
      Leu Gly Phe Leu Gly Asp
                         485 486
                                     CLONE C8.6
      G GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
           Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
40
                                                   .10
      TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
                                      20
                15
       AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
      Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                        30
       AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
       Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
50
           40
       TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
       Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
       GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
       Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
                           : :: 70
       TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 27.1
       Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
                                      85
                 80
       ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
       Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
                                              100
                         95
       AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
       Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
                                                      115
                                110
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AGA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
      Arg Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
                                       125
      GAT AAG GGG AAA AAA GAA TAT GGA TTG TTT TAT AAA CTT 427
      Asp Lys Gly Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
                          135
                                               140
      GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
      Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
              145
                                   150
10
      ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
      lle Ser Cys Asn Thr Ser Val Ile Thr Gin Ala Cys Pro
                      160
                                           165
      AAG GTA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC 544
      Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
15
                               175
      CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
      Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
                  185
                                       190
      TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGG ACA GTA 622
20
      Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Arg Thr Val
                          200
                                               205
      CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
      Gin Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gin
              210
                                   215
      CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
25
      Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
                     225
                                          . 230
      ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
.3.0
        . 235
                              240
      ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
      The Val Gin Leu Asn Glu Ser The Val He Asn Cys Thr
                  250
                                       255
      AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
      Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
35
                          265
      CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
      Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
                                   280.
40
      GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
      Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
                      290
                                           295
      TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
      Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
                              305
      GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
      Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
                  315
                                       320
      TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
50
      Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
                          330
                                               335
      TGT GGA GGG GGA TTT TTC TAC TGT AGT ACG AGA AAA CTG 1051
      Cys Gly Gly Phe Phe Tyr Cys Ser Thr Arg Lys Leu
              340
                                 345
      TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
                      355
                                           360
      ACC GGG GAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
      Thr Gly Asp Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
60
                              370
                                                 375
      TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
      Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
                                       385
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GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
     Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
                         395
                                             400
     390
     AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA AGG AGA 1246
   Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Arg Arg
                                 410
             405
     GAT GGT GGA AGT AAC ACC AGT GAC AAC CAG ACT GAG ACC 1285
     Asp Gly Gly Ser Asn Thr Ser Asp Asn Gln Thr Glu Thr
                                         425
                     420
     TTT AGA CCT GGG GGA GGA GAT ATG AGG GAC AAG TGG AGA 1324
     Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Lys Trp Arg
                                                 440
                             435
         430
     AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
     Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
                                     450
     TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
     Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
                                             465
                         460
     455
     CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
     Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
20
             470
     CTT AGG TTC TTA GGA GAT AAA GCT TCT AGA GTC 1474
     Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
                     485
                                 CLONE C15.2
         CTC GAG GTA CCT GTA TGG AAA GAA GCA ACT ACC ACT 36
         Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
30 CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
     Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
                                  -20
     AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
     Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
      GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
      Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
                                                  50
                               45
      GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
      Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
                                      60
                  55
      ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
      Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
                           70
      AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
      Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
                                  85
               80
      AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
      Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
                                         100
50
      AGT AGT GCC ACT ACC AAT AGT AGT TGG GAA GAA ATG 348
      Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
                              110
         105
      AAG GGG GAA ATG AAA AGA TGC TCT TTC AAT ATC ACC ACA 387
      Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
55
                  120
      AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
      Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
                          135
      TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
      Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
                                   150
              145
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ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
      Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
                       160
                                           165
      CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
      Gin Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
          170
                              175
      CAT TIT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
      His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
                  185
                                      190
      AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
      Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
                          200
      GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
      Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
15
              210
                                  215
      GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
      Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu-
                       225
      GAA GAG GTA ATA ATT AGA TCT GAC AAT ATC ACA GAC AAT 738
     Glu Glu Val Ile Ile Arg Ser Asp Asn Ile Thr Asp Asn
      235
                              240
                                                   245
      ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
Thr Lys Thr Ile Ile Val Gin Leu Asn Glu Ser Val Val
                                      255
25
     ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA AGA AAA AGT 816
      Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser
                          265
                                               27Ô
      ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
     The His The Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
             275
                                  280
                                                       285
      GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
      Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
                      29.0
                                           295
      AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
35
      Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
        300
                              305
                                                   310
     ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
     Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
                  315
                                      320
40
      AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
      Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
                          330
                                             335
     GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
     Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
45
              340
                                  345
      TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
     Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
                      355
                                          360
     AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
50
     Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
         3.65
                              370
     ACA GGA GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
     Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
                  380
                                      385
55
     CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
     Gin Tie Tie Asn Met Trp Gin Glu Val Gly Lys Ala Met
                          395
                                               400
     TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
     Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
60
             405
                                  410
     AAC ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
     Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
                      420
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AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
Lys Asn Glu Ser Il Thr Thr Glu Val Phe Arg Pro Gly
                               435
      GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
      Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
                                        450
                   445
      AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
      Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
                           460
      CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
      Pro Thr Lys Ala Lys Arg Arg Val Val Gin Arg Glu Lys
               470
      AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
      Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
                                             490
                       485
      TTG GGA GCA TAA AGC TTC TAG AGT CGA CCT GCA 1512
      Leu Gly Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
                               500
                                    CLONE C15.3
20
          CTC GAG GTA CCT GTG TGG AAA GAA GCA ACT ACC ACT 36
          Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
                                                  . 10
      CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
      Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
                                     20
      AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
      Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                                             35
                        30
      GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
      Asp Pro Asn Pro Gin Glu Val Val Leu Gly Asn Val Thr
                                 45
      GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
                                         60
3.5
      ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
       Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
      AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
      Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
40
                                      85
                80
      AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
                                             100
                         95
      AGC AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
      Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
                                110
      AAG GGG GAA ATG AAA AGG TGC TCT TTC AAT ATC ACC ACA 387
      Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
                                         125
50
                   120
       AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
      Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
                                                 140
                            135
       TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
       Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
55
                                    150
       ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
               145
       Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
                        160
      CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
       Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
                                175
       CAT TIT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
       His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
                                         190
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AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
                              200
       GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660.
       Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
                210
                                        215
       GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
       Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
                        225
                                                230
       GAA GAG GTA ATA ATT AGA TCT GGC AAT ATC ACA GAC AAT 738
       Glu Glu Val Ile Ile Arg Ser Gly Asn Ile Thr Asp Asn
                                   2:40
       ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
       Thr Lys Thr Ile Ile Val Gin Leu Asn Glu Ser Val Val
15
                    250
                                            255
       ATT AAT TGT ACA AGA TCC AAC AAC AAT ACA AGA AAA AGT 816
Ile Asn Cys Thr Arg Ser Asn Asn Asn Thr Arg Lys Ser
                                                    . 270
       ATA CAT ATA GGA CCA GGG AGT GCA TIT TIT GCA ACA GGA 855
20
       Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
              275
                                       280
       GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894 Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
                         290
                                                295
25
       AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
       Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
          300
                                   305
       ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
       Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
                    315
                                            320
       AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
       Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
                              330
                                                     3:35
       GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
35
       Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
                340
                                       345
                                                              350
      TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
                         355
                                                360
40
       AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
       Asn Val The Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
      365 370 375
ACA GGG GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
Thr Gly Asp Glu Asn Tie lie Leu Pro Cys Arg Ile Lys
45
                    380
                                            385
      CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
390 395 400
       TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
50
       Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
                                      410
                                                              415
      AAT ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT AGT 1284
      Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser-
                         420
                                                425
55
      AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
      Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
                                 435
                                                        440
      GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
      Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
                    445
                                           450
      AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
      Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
                        460
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CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
     Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
                                                               had a time
                                    475
     AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
     Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
                       485
      TTA GGA GCA TAA AGC TTC TAG A 1501
Leu Gly Ala Xaa Ser Phe Xaa
10
                                      CLONE C7.2
      GG GAA TTC GGA TCC GGG GTA CCT GTG TGG AAG GAA GCA 38
          Glu Phe Gly Ser Gly Val Pro Val Trp Lys Glu Ala
      ACC ACC ACT CTA TTC TGT GCA TCA GAT GCT AGA GCA TAT 77
      Thr Thr Thr Leu Phe Cys Ala Ser Asp Ala Arg Ala Tyr
      GAC ACA GAG GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT 116
      Asp Thr Glu Val His Asn Val Trp Ala Thr His Ala Cys
                        .30
20
      GTA CCC ACA GAC CCT AGT CCA CAA GAA GTA GTT TTG GAA 155
Val Pro Thr Asp Pro Ser Pro Gln Glu Val Val Leu Glu
                                 45
      AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG 194
      Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met
25
                                          60
                    55
      GTA GAA CAA ATG CAT GAG GAT ATA ATT AGT TTA TGG GAT 233
      Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
                             70
      CAA AGC TTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT 272
30
      Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys
                80
      GTT ACT TTA AAT TGC AGT GAT TAT AGG AAT GCT ACT GAT 311
      Val Thr Leu Asn Cys Ser Asp Tyr Arg Asn Ala Thr Asp
                                              100
35
      TAT AAG AAT GCT ACT GAT ACC ACT AGT AGT AAC GAG GGA 350
      Tyr Lys Asn Ala Thr Asp Thr Thr Ser Ser Asn Glu Gly
                                 110
       AAG ATG GAG AGA GGA GAA ATA AAA AAC TGC TCT TTC AAT 389
       Lys Met Glu Arg Cly Glu Ile Lys Asn Cys Ser Phe Asn
                                          125
                   120
       ATT ACC ACA AGC ATA AAA AAT AAG ATG CAG AAA GAA TAT 428
       Ile Thr Thr Ser Ile Lys Asn Lys Met Gln Lys Glu Tyr
                                                  140
                            135
       130
       GCA CTT TTC TAT AAA CTT GAT ATA GTA CCA ATA GAT AAT 467
       Ala Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asn
               145
                                    1.50
       ACA AGC TAT ACA TTG ATA AGT TGT AAC ACC TCA GTC ATT 506
Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr Ser Val Ile
                                              165
                        160
 50
       ACA CAG GCC TGT CCA AAG GTA TCC TTT GAA CCA ACT CCC 545
Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Thr Pro
                                                      180
                                 175
           170 -
       ATA CAT TAT TGT GCT CCG GCT GGT TTT GCG ATT CTA AAG 584
       Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys
                                          190
                    185
       TGT AAT GAT AAG AAG TTC AGT GGA AAA GGA GAA TGT AAA 623
       Cys Asn Asp Lys Lys Phe Ser Gly Lys Gly Glu Cys Lys
                             200
       195
       AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA 662
 60
       Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro
                                      215
                210
       GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA 701
       Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
                                              2:30
                        225
 65
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GAA GAA GAG GTG GTA ATT AGA TCT GAC AAT TTC ATA GAC 740
       Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Ile Asp
                               240
                                                     245
       AAT ACT AAA ACC ATA ATA GTA CAG CTG AAA GAA TCT GTA 779
       Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val
                   250
                                        255
      GAA ATT AAT TGT ATA AGA CCC AAC AAT AAT ACA AGA AAA 818.
Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys
                            265
                                                270
10
       GGT ATA CAT ATA GGA CCA GGG AGA GCA TGG TAT GCA ACA 857
      Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr
               275
                                    280
                                                         285
      GGA GAA ATA GTA GGA GAT ATA AGA AAG GCA TAT TGT AAC 896
      Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn
15
                       290
                                            295
      ATT AGT AGA ACA AAA TGG AAT AAC ACT TTA ATA CAG ATA 935
      Ile Ser Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile
          300
                                305
                                                     310
      GCT AAC AAA TTA AAA GAA AAA TAT AAT ACA ACA ATA AGC 974
20
      Ala Asn Lys Leu Lys Glu Lys Tyr Asn Thr Thr Ile Ser
                   315
                                        320
      TTT AAT CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ACG 1013
      Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Thr
                           330
                                                335
25
      CAT AGT TTT AAT TGT GGA GGG GAG TTT TTC TAC TGT GAT 1052
      His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asp
                                    345
      TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT TTA AAT GGT 1091
Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly
30
                       355
                                            360
      ACT TGG AAT TTT ACT GCA GGG TCA AAT GAA ACT GAA GGC 1130
      Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly
          365
                               370
                                                     375
      AAT ATC ACA CTC CCA TGC AGA ATA AAA CAA ATT ATA AAC 1169
35
      Asn Ile Thr Leu Pro Cys Arg Ile Lys Gin Ile Ile Asn
                   380
      AGG TGG CAG GAA GTA GGG AAA GCA ATG TAT GCC CCT CCC 1208
      Arg Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro
      390
                           395
                                                400
40
      ATC AGT GGA CAA ATA AAA TGC TCA TCA AAC ATT ACA GGG 1247
      Ile Ser Gly Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly
405 410 415
      ATG ATA TTA ACA AGG GAT GGT GGT AAC GAG AAC AAT AAT 1286
      Met Ile Leu Thr Arg Asp Gly Gly Asn Glu Asn Asn Asn
45
                      420
                                            425
      GAG AGC AGT ACT ACT GAG ACC TTC AGA CCG GGA GGA 1325
      Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly Gly
         430
                              :435
      GAT ATG AGG AAC AAT TGG AGA AGT GAA TTA TAT AAA TAT 1364
50
      Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
                  445
                                      450
      AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC 1403
      Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr
                           460
                                               465
5.5
      AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA AGA GCA 1442
      Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala
              470
                                   475
                                                        480
      GTG GGA GCG CTA GGA GCT ATG TTC CTT GGG TTC TTA GGA 1481
      Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly
60
                      485
                                           4.90
      GCA TAA AGC TTC TAG ACC GAC TCT AGA GGA TCC 1514
      Ala Xaa Ser Phe Xaa Thr Asp Ser Arg Gly Ser
                               500
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<u>CLONE C7.10</u>
      G GTA CCT GTG TGG AAG GAA GCA ACC ACC ACT CTA TTC 37
        Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
      TGT GCA TCA GAT GCT AGA GCA TAT GAC ACA GAG GTA CAT 76
      Cys Ala Ser Asp Ala Arg Ala Tyr Asp Thr Glu Val His
                                   20
                                                        25
      AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC CCT 115
      Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
1.0
                       30
      AGT CCA CAA GAA GTA TTT TTG GGA AAT GTG ACA GAA AAT 154
      Ser Pro Gln Glu Val Phe Leu Gly Asn Val Thr Glu Asn
      TTT AAT ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG TAT 193
      Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met Tyr
15
                                        60
      GAG GAT ATA ATT AGT TTA TGG GAT CAA AGC TTA AAG CCA 232
      Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
      TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
      Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
                                    85
               80
      AGT GAT TAT AGG AAT GCT ACT GAT TAT AAG AAT GCT ACT 310
      Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys Asn Ala Thr
                                           100
25
                       95
      GAT ACC ACT AGT AGT AAC GAG GGA AAG ATG GAG AGA GGA 349
      Asp Thr Thr Ser Ser Asn Glu Gly Lys Met Glu Arg Gly
                              110
                                                   115
      GAA ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC ATA 388
      Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile
                                       125
                  120
      AAA AAT AAG ATG CAG AAA GAA TAT GCA CTT TTC TAT AAA 427.
      Lys Asn Lys Met Gln Lys Glu Tyr Ala Leu Phe Tyr Lys
                          135
                                                140
      CTT AAT ATA GTA CCA ATA GAT AAT ACA AGC TAT ACA TTG 466
      Leu Asn Ile Val Pro Ile Asp Asn Thr Ser Tyr Thr Leu
                                   150
              1,45
      ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
      Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
                      160
                                           165
      AAG GTA TCC TTT GAA CCA ATT CCC ATA CAT TAT TGT GCT 544
      Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
                               175
                                                    180
         170
      CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG AAG 583
      Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys
                                       190
                  185
      TTC AGT GGA AAA GGA GAA TGT AAA AAT GTC AGC ACA GTA 622
      Phe Ser Gly Lys Gly Glu Cys Lys Asn Val Ser Thr Val
                          200
                                               205
      CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT CAA 661
50
      Gin Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gin
                                   215
              210
      CTG CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTG GTA 700
      Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val
                      225
                                           230
      ATT AGA TCT GAC AAT TTC ACA GAC AAT ACT AAA ACC ATA 739
Ile Arg Ser Asp Asn Phe Thr Asp Asn Thr Lys Thr Ile
                               240
      ATA GTA CAG CTG AAA GAA TCT GTA GAA ATT AAT TGT ATA 778
      Ile Val Gln Leu Lys Glu Ser Val Glu Ile Asn Cys Ile
                  250 -
                                      255
      AGA CCC AAC AAT AAT ACA AGA AAA GGT ATA CAT ATA GGA 817
      Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Ile Gly
                          265
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CCA GGG AGA GCA TGG TAT GCA ACA GGA GAA ATA GTA GGA 856
       Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu II Val Gly
               275
                                    280
       GAT ATA AGA CAG GCA TAT TGT AAC ATT AGT AGA ACA AAA 895
       Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys
                       290
                                            .295
       TGG AAT AAC ACT TTA ATA CAG ATA GCT AAC AAA TTA AAA 934
       Trp Asn Asn Thr Leu Ile Cln Ile Ala Asn Lys Leu Lys
                                .30.5.
                                                    310
       GAA AAA TAT AAT ACA ACA ATA AGC TTT AAT CGA TCC TCA 973
10
       Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser
                   315
       GGA GGG GAC CCA GAA ATT GTA ACC CAT AGT TIT AAT TGT 1012
       Gly Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys
15
                           330
                                                335
      GGA GGG GAA TTT TTC TAC TGT AAT TCA ACA CAA CTG TTT 1051
      Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe
               340
                                    345
      AAT AGT ACT TGG AAT TTA AAT GGT ACT TGG AAT TTT ACT 1090
Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp Asn Phe Thr
20
                       355
                                           360
      GCA GGG TCA AAT GAA ACT GAA GGC AAT ATC ACA CTC CCA 1129
      Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu Pro
          365
                               370
                                                    375
      TGC AGA ATA AAA CAA ATT ATA AAC AGG TGG CAG GAA GTA 1158 Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val
                   380
                                        385
      GGA AAA GCA ATG TAT GCC CCT CCC ATC AGT GGA CAA ATA 1207
      Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile
3.0
      390
                           395
                                                400
      AGA TGC TCA TCA AAC ATT ACA GGG ATG ATA TTA ACA AGG 1246
      Arg Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg
              405
                                   410
      GAT GGT GGT AAC GAG AAC AAT AAT GAG AGC AGT ACT ACT 1285
3.5
      Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr
                       420
                                            425
      GAG ACC TTC AGA CCG GGA GGA GGA GAT ATG AGG AAC AAT 1324
      Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn
          430
                               435
                                                    440
      Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile
                  445
                                       450
      GAG CCA TTA GGA GTA GCA CCC ACC GAC TCT AGA GGA TCC 1402
      Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg Gly Ser
      455
                           460
      TCT AGA 1408
      Ser Arq
          469
50
                                    CLONE C11.5
          GAG GTA CCT GTG TGG AAA GAA GCA ACC ACT ACT CTA 36
          Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
      TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GGG GTG 75
     Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Gly Val
               15.
                                    20
      CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
     His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
     CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
     Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
          40
                               45
                                                   50
     GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
      Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
                                        60
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. : :	م	CA	TGT	GTA	AAG	TTA	ACC	CCA	CTT	TGT	GTT	ACT	CTA	AAC	270
- 5	P	ro	Сув	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	
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٠.	G	CC.	105	ACT	AGT	AGC	GAG	GAA	AAG	ATG	GAG	AAG		GAA	387
	A	la	Thr	Thr	Ser	Ser	Glu	Glu	Lys	Met	Glu	Lys	Gly	Glu	
15					120				. '	125	No.	5.3			A26
٠.	λ	TA	AAA	AAC	TGC Cys	TCT	TTC	AAT	TIE	The	Thr	His	Met	AAA	420
	. 1	30					135					140		*	
	G	ÀΤ	AAG	GCA	CAG	AAA	GAA	TAT	GCA	CTT	TTT	TAT	AAA	CTT	465
20) A	sp	Lys		Gln	Lys	Glu	Tyr			Phe	Tyr	Lys	Leu 155	
٠.,		N TT	המיזה	145.	CCÀ	474	CAT	CAT	150 AAT	AAT	GCC	AGC	TAT	AGG	504
	A	SD	Ile	Val	Pro	Ile	Asp	Asp	Asn	Asn	Ala	Ser	Tyr	Arg	
						160			: :	0.1	165				
25	5 " T	TG	ATA	AGT	TGT	AAT	ACC	TCA	GAC	ATT	ACA	CAG	GCC Ala	TGT	543
. :-	. <u>.</u> L	eu	11e	Ser	Cys	ASN	Fnr	175	ASD	116	****	3,111	180	9,9	
	c	CA.	AAG	GTG.	ACC	TTT	GAG	CCA	ATT	ccc	ATA	CAT	TAT	TGT	582
erior	P	ro	Lys	Val	Thr	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	
3.0)		-		185	mmm	céc	ስ ጥጥ	CTA	190	тст	444	CAT	AAG	621
٠	. : 2	la	Pro	Ala	Cly	Phe	Ala	Ile	Leu	Lys	Сув	Lys	Asp	Lys	
٠.٠	1	95					200					205	. • '		
		AG	TTC	AAT	GGA	ACA	GGA	CCA	TGT	TCA	AAG	GTC	AGC	ACA	660
3.5	L	ys	Phe	210	Gly	Thr	GIY	Pro	215	ser	Lys	vai	Jer	220	
		TA.	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	GTA	GTA	TCA	ACT	699
.,,,,,,,	V	al	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	
						225					230		.:		738
4:() (AA	CTG	TTG	TTA	AAT	Clv	Ser	Leu	Ala	Glu	Glu	Glu	GTA Val	
			235	14				240					245		
	Ç	TA	דיד מ	AGA	TCT	GTC	AAT	TTC	ACA	GAC	AAT	GCT	AAA	ATC	777
		al	Ile	Arg	Ser	Val	Asn	Phe	Thr	255	Asn		Lys	Ile	
4	,	ATA	ATA	CTA	250 CAG	CTG	AAA	GAA	CCT	GTA	GCA	ATT	AAT	TGT	816
		lle	Ile	Val	Gln	Leu	Lys	Glu	Pro	Val.	Ala	ile	Asn	Cys	
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		GA	CCA	GGG	AGC	ACA	TTT	TAT	ACA	ACA	GGA	GAA	ATA	ATA	894
1,1		Gly	Pro	Gly	Ser	Thr	Phe	Tvr	Thr	Thr	Gly	Glu	Ile	TIE	**!
5	5 (ica	CAC	מדמ	ACA	290	GCA	TAT	TGC	AAG	ATT	AGT	AAA	GAA	933
٠.	, ,	Glv	Asp	Ile	Arg	Lys	Ala	Tyr	Сув	Lys	Ile	Ser	Lys	Glu	
eii t			200	2 1 1				305		11 11 11			3:10		
·		AAA	TGG	AAT	AAC	ACT	TTA	AGA	CAG	GTA	GTT V=1	AAA	AAA	Leu	972
6	n :				315		'		·	320				Leu	
	. 1	ADA	CAA	CAA	TITT	GGG	AAT	AAA	CACA	ATA	ATT	TTT	AAT	CGA	1011
		Arg	Glu	C1n	Phe	:Glv	Asn	Lvs	Thr	Ile	Ile	Phe	Asn	Arg	
		325					330				i	335			

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TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
Ser Ser Gly Gly Asp Pro Glu Ile Val Met His S r Phe
               340
                                     345
       AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
       Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
                        355
                                             360
       CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
       Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
                                370
 10
       AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167.
       Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg.
                   380
                                         385
       ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206.
       The Lys Gln Tie Tie Asn Met Trp Gln Glu Val Gly Lys
15
                            395
                                                 400
       GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
       Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
               405
                                    4:10
                                                         415
       ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
20
       Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
                       420
                                            425
       GGT AGG AAT GTC ACA AAC AAT ACC GAA ACC TTC AGA CCT 1323
       Gly Arg Asn Val Thr Asn Asn Thr Glu Thr Phe Arg Pro
          430
                                435
      GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
25
      Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
                  445
      TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
      Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
3.0
      455
                            460
                                                465
      GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
      Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
                                    475
      AAA AGA GCA GCA CTA GGA GCC TTG TTC CTT GGG TTC TTA 1479
35
      Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
                       485
      GGA GCA TAA AAG CTT CTA GA 1499
      Gly Ala Xaa Lys Leu Leu
       495
40.
                                    CLONE C11.7
          GAG GTA CCT GTA TGG AAA GAA GCA ACC ACT ACT CTA 36
          Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
      TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
      Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
              . 1:5
                                     20
      CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114-
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
50
                        30
      CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
      Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
          40
                                45
      GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
      Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
                                         60
                   . 55
      CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA AGC CTA AAG 231
      His Glu Asp Ile Ile Ser Leu Trp Asp Clu Ser Leu Lys
60
      CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
      Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
                                    85
      TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
      Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
6:5
                      95
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ART ACT ART TCC ACT ART ACT ACT TCC TCT ACT CCT ACG 348
     Asn Thr Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr
                             110
       105
     GCC ACT ACT AGT AGC GAG GAA AAG ATG GAG AAG GGA GAA 387
     Ala Thr Thr Ser Ser Glu Glu Lys Met Glu Lys Gly Glu
                                     125
                 120
     ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA CAC ATG AAA 426
     Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr His Met Lys
                                              140
     130
                         135
     GAT AAG GTA CAG AAA GAA TAT GCA CTT TTT TAT AAA CTT 465
     Asp Lys Val Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
                                                     155
                                 150
     GAT ATA GTA CCA ATA GAT GAT AAT AAT ACC AGC TAT AGG 504
     Asp Tle Val Pro Tle Asp Asp Asn Asn Thr Ser Tyr Arg
                                         165
                     160
15
     TTG ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT 543
     Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
        170 / ....
                             175
     CCA ATG GTG ACC TTT GAG CCA ATT CCC ATA CAT TAT TGT 582
    Pro Met Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys
                                      190
                 185
    GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
     Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
                         200
     AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
     Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
                                                      220
                                  215
             210
     GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
      Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
                                          230
                     2.25
     CAA CTG TTG TTA AAT GGC AGT CTT GCA GAA GAA GAA GTA 738
      Gln Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
                                                 245
                             240
      GTA ATT AGA TCT GTC AAT TTC ACA GAC AAT GCT AAA ATC 777.
      Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
35
                                      255
                 250
      ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
      Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
                                              270
                         265
      260::
      ACA AGA CCC AAC AAC AAT ACA AGA AAA GGT ATA CAT CTA 855
      Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
                                  280
      GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
      Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
                                          295
                     290
45
      GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
      Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
          300
                              305
      AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
      Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
                                      320
                  315
      AGA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
      Arg Glu Glm Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
                                              335
                          330
      TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
      Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
                                  345
      AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
      Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
                                         360
      CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
      Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
                              370
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AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
Ser Thr Glu Gly Asn Ser Thr II Thr Leu Pro Cys Arg
                   .380∶
                                         385
       ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
                            395
                                                 400
       GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
       Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
               405
                                    410
                                                          415
       ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
       Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
                       420
                                             425
       GGT AGG AAT GTC ACA AAC AAT ACC GAN NCC TTC AGA CCT 1323
       Gly Arg Asn Val Thr Asn Asn Thr Xaa Xaa Phe Arg Pro
 15
                                435
                                                     440
       GGA GGA GGC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
       Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
                   445
                                        450
       TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
 20 -
       Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
       455
                           460
                                                 465
       GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
       Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
               470
                                    475
       AAA AGA GCA GCA CTA GGA GCT TTG TTC CTT GGG TTC TTA 1479
       Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
                       485....
       GGA GCA TAA AAG CTT CTA GA 1499
       Gly Ala Xaa Lys Leu Leu
         495
3:0
                                    CLONE C10.5
          GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
          Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
35
                                                 10
      TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
      Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
                                     20
      AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
      Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                        30
                                             35
      AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
      Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
          40
                                45
      TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
      Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
                   55
      GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
      Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
50
                            70
      TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
      Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
              -80
                                   85
      AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
      Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
                       95
                                           100
      ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
      Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
                               110
                                                    115
      ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
      Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
                  120
                                       :125
      AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
     Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
65
      130
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GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
     Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
                                  150
                                                       155
     TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
     Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
                                          165
                     160
     CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
                                                   180
                              175
     GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
10
     Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
                                      190
                  185
     AAG TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA 622
     Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
                          200
15
     GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
     Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
              210
                                   215
     CAA CTG TTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTA 700
     Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
20
                      225
                                           230
      GTA ATC AGA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
      Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
                               240
     ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
     Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
                                       255
                  250
     ACA AGA CTT GGC AAC AAT ACA AGA AAA AGT ATA AAT ATA 817
      Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
30
                           265
      GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
      Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
                                   280
      GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT AGT AGA GCA 895
      Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
35
                                           295
                      290
      CAA TGG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAA TTA 934
      Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
                                                   310
      AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
40
      Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
                                       320
                  31:5
      CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
      Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
                                               3:35:
45
                           330
      3:2:5
      TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
      Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
              340
                                   345
      CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
      Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
                       355
                                           360
      CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
      Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
                               370.
         365
      AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
      Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
                                       385
      ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
      Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
                                               400
                           395
      TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
      Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
                                   410
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AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
       Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
                       420
                                            425
       ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
       Tie Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
           430
                               435
       Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
                   445
                                       450
       CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
       Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
                           460
       GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
       Val Gin Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
15
               470
                                   475
       TTC CTT GGG T TCTTAGGAG CATAAAGCTT CTAGA 1475
       Phe Leu Gly
20
                                   CLONE C10.7
      G GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
       Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
                                                1.0
       TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
25
      Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
               15
                                    20
      AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
      Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                       .30
      AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
30
      Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
          ...40
      TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
      Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
35
                                        60
      GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
      Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro-
                           - 70
      TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
      Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
40
               - 80
                                    85
      AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
      Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
                       95
                                          100
      ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
      Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
      ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
      Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
50
                  120
                                       125
      AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
      Lys Val Gin Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
      130
                          135
                                              140
      GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466 Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
55
              1.45
                                  150
      TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
                      160
      CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
      Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
         170
                              175
                                                  1.80
      GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
      Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
65
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	AAG	TTC	AAT	GGA	ACA	GGA	CCA	TGT	AAA	AAT	GTC	AGC	ACA	622
	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	Asn	Val	ser	Thr	
	195					200					205	TO N	D.CT	661
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	CAA	CTG	TTG	TTA	AAT	GGC	AGT	CTA	GCA	GAA	GAA	GAG	GTA	7.00
	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	val	
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10	GTA	ATC	AGA	TCT	GCC.	AAT	TTC	ACA	GAC	AAT.	GCT	AAA	The	739
er Service	vaı	235	Arg	Ser	Ala	Asn	240	THE	Asp	no	n.a	245	1112.	
	מדם	ATA	GTA	CAT	CTA	AAT		ACT	GTA	AAA	ATT		TGT	778
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	ACA.	AGA	CTT	GGC	AAC	TAA	ACA	AGA	AAA	AGT	ATA	AAT	ATA	817
			Leu-	Gly	Asn	Asn	Thr	Arg	Lys	Ser	11e	Asn	TT6.	
	260	CCN	CCC.	n C h	CTD	265 CTC	ጥልጥ	GCA	ACA	GGA			ATA	856
20	Glv	Pro	Glv.	Ara	Val	Leu	Tyr	Ala	Thr	Gly	Glu	He	Ile	
	8		275		•			280	1				285	•
	GGA	GAC	ATA	AGA	CAA	GCA	CAT	TGT	AAC	ATT	AGT	AGA	GCA	895
1	Gly	Asp	Ile	Arg		Ala	His	Cys	Asn		Ser	Arg	Ala	٠.
0.5					290	mm 2	C B:B	D-D-C	GTA	295	CAC	AAG	ב דד	974
25	CAA	TGG	AAT	AAG	ACI	TAN	GAA	LVS	Val	Val	ASD	LVS	Leu	
		300					305	•				310		
	AGA	AAA	CAA	TTT	GGG	GAT	AAT	ACA.	ACA	ATA	GCT	TTT	AAT	973
	Arg	Lys	Gln	Phe	Gly	Asp	Asn	Thr	Thr	Ile	Ala	Phe	Asn	
30	1262			3.15				C 3 'S	320	CTA	ATC	CAC	 ДСТ	1012
	CGA	TCC	TCA	GGA	GGG	GAC	Dro	GAA	Ile	Val	Met	His	Thr	1012
	325		set	Gry	GIY	330	, 10	GIG		•	335			
	THE	TAA	TGT	GGA	GGG	GAA	TTT	TTC	TAC	TGT	AAT	ACA	ACA	1051
3.5	Phe	Asn	Cys	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	Thr	Thr	
None of			340					345			.:*.	: 11 .	350	1000
	CAA	CTG	TTT	AAT	AGT	ACT	TGG	AAT	AAT	ACT	166	TVE	GAI	1090
· · · · · · · · · · · · · · · · · · ·	GIN	Leu	Pne	Asn	355	Thr.	irp	ASI	Asn	360	110	Lys	nsp	
4.0	CCT	AAC	AGG	AGT	GAC	AAT	ATC	ACA	CTC	CCA	TGC	AGA	ATA	1129
g Jillya kur	Pro	Asn	Arg	Ser	Asp	Asn	Ile	Thr	Leu	Pro	Cys	Arg	Ile	
		365					370			in the late	16-61	375		1160
de de la companya de	AAA	CAA	ATT	ATA	AAC	ATG	TGG	CAG	GAA	Ual	GGA	TUE	A I a	1168
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i de et di	Met	Tyr	Ala	Pro	Pro	Ile	Arg	Gly	Glu	Ile	Arg	Cys	Ser	
	300	_		• 1		395		٠.			400	: :		1246
	TCA	TAA	ATC	ACA	GGG	CTC	CTA	CTA	ACA	AGA	GAT	Clar	GGT	1246
50	Ser	Asn		Thr	GIA	Leu	ren	410	Thr	ALG	usb	GIY	415	y .
	דבב	GAC	405 GAT	GGT	AAT		ACG			AAC	AGG	ACC		1285
	Asn	Asp	Asp	Gly	Asn	Asp	Thr	Thr	Thr	Asn	Arg	Thr	Glu	
	1 1 1		. :	·	420	* * **		1 1 1		425	arti i di		:::: '	
55	ATC	TTC	AGA	CCT	GGA	GGA	GGA	GAT	ATG	AGG	GAC	AAT	TGG	1324
741 T +	Ile			Pro	Gly	Gly	Gly	Asp	Met	Arg	ASD	440	irp	4 t iii
	מיאמי	430	CAN	ጥጥን	ጥልጥ	ACA	435 TAT	AAA			AAA			1363
	Ara	Ser	Glu	Leu	Tvr	Ara	Tyr	Lys	Val	Val	Lys	Ile	Glu	
60				445	·				450		11. 11			
	CCA	TTA	GGA	ATA	GCA	CCC	ACC	AGG.	GCA	AAG	AGA	AGA	GTG	1402
		Leu	Gly	.I l:e	Ala			Arg	Ala	Lys	465	Arg	vaı	
	455					460								

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GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
      Val Cln Arg Clu Lys Arg Ala Val Cly Leu Cly Ala Leu
                                   475
      TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1475
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
                                   CLONE C17.1
          CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
          Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
                                               10
      CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG 75
      Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
                                     20 -
      GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA 114
      Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr.
                        30
      GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
      Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
20
                                4.5
      GAA AAT TIT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
      Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gin
                   55
                                        60
      ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
      Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
                            70
      AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
      Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
              80
                                    85
      AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
                        95
      ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
      Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
         105
                               110
      ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
      Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
                  120
                                        125
      CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
      Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
                         135
                                                140
      AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
      Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
            145
                                   150
      ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
      Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
                      160
      CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
      Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
        170
                               175
                                                    .180
      AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
      Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
      185
ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
      Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
      195 200 205 CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
      Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
              .210
                                   215
     GCA GAA GAA GAC ATA GTA ATT AGA TOO GCC AAT CTC ACA 699
      Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
                      225
                                            230
      GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
      Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser-
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	GTA	ACA	ATG	AAT	TGT	ACA	AGA	CCC	AAC	AAC	AAT	ACA	ATG	777
	val	Thr	Met	250	Cys	Int	Arg	Pro	255	ASII	Asn	LHE	Mec	
	AAA	AGT	ATA	CAT	ATA	GGA	CCA	GGC	AGA	GCA	TTT	TAT	GCA	816
***	Lys 260		Ile	His	Ile	Gly 265	Pro	Gly	Arg	Ala	270	Tyr	Ala	
ggyvang amilian kidig. Bilingga Biling aliking	ACA	GGA	AAC	ATA	ATA	GGA	GAT	ATA	AGA	CAA	GCA	CAT	TGT	855
parapytrauld (1971) External (1971)	Thr	Cly		Ile	Ile	Gly	Asp		Arg	Gln	Ala	His	285	.*
10	AAC	ATT	275 AGT	ĞĞA	ACA	AAA	TGG	280 AAT	GAC	ACT	TTG	AAA		894
	Asn	Ile	Ser	Gly	Thr	Lys	Trp	Asn	Asp	Thr	Leu	Lys	Lys	•
	ATA	GCT	ATA	AAA	290	AGA	GAA	CAA	TTT	295 AAT	AAG	ACA	ATA	933.
	Ile	Ala	Ile	Lys	Leu	Arg	Glu	Gln	Phe	Asn	Lys	Thr	Ile	
15	GTC	300	דממ	CAA	بيندر	TCA	305 GGA	GGG	GAC	CCA	GAA	310	GCA	972
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			340					345					350	1000
25	GGG	Ser	AAT	AAC Asn	Thr	Lys	GLV	AAI	Asp	Thr	Ile	Thr	Leu	1089
그렇다는 1					355					360	40.46			1120
	CCA	TGC	AGA	ATA	AGA	Gln	Ile	Ile	AAC	Met	Trp	Gln	LVS	1128
30		365	_				370			200	3	.375.		
	ATA	GGA	AAA	GCA	ATG	TAT	GCC	CCT	CCC	ATC	AAA Lys	GGG	CAA	1167
				380	**				385		, :: : ::	:	. :	,
2=	ATT	AGA	TGT	TCA	TCA	AAT	ATT	ACA	GGG	CTA	ATA	TTA	ACA	1206
3.5	390		• .		•	395					11e	ina in		
 Parking to the company	AGA	GAT	GGT	GGT	AAC	AAC	AAC	ATG	AGC	AAG	ACC	ACC	GAG.	1245
	Arg	Asp	405	GLY	Asn	.ASR	ASN	410	ser	Lys	Thr		415	·
40	ACC	TTC	AGA	CCT	GGA	GGA	GGA	GAT	ATG	AGG	GAC	AAT	TCC	1284
	Thr	Phe	Arg.	Pro	G1y	Gly	Gly	Asp	Met	425	Asp	ASN	rrp	
	AGA	AGT	GAA	TTA	TAT	AAA	TAT	AAA	GTA	GTA	AAA	ATT	GAA	1323
4.5	Arg	Ser 430	Glu	Leu	Tyr	Lys	Tyr 435	Lys	Val	VAI	Lys	440	GIU	
	CCA	TTA	GGA	GTA	GCA	CCC	ACC	AGG	GCA	AAG	AGA	AGA	GTG	1362
	Pro	Leu		Val 445		Pro	Thr	Arg	Ala 450		Arg	Arg	Val	• • • • • •
jogađenija. Programa Programa	GTG	CAG	AGA	GAA	AAA	AGA	GCA	GTG	GGA	ATA	GGA	GCT	GTG	1401
50	Val			Glu		Arg 460	Ala	Val	Gly	Ile	Gly 465		Val	
	TTC	CTT	GGG	TTC			GCA	TAA	AGC	TTC	TAG		435	·
	Phe	Leu	Gly	Phe	Leu	Gly	Ala	Xaa	Ser	Phe	Xaa 478	ili.		
55			470				•	473		·	4.70			
Billianur (mmuzi) Gurakia minaka						C.D.C.	mcc.	CLO	VE C	17.3	200) CC	N.C.T	16
		Leu	GAG	Val	Pro	Val	Trp	Lys	Glu	Ala	ACC Thr	Thr	Thr	2,0
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60	Leu	TTT	TGT.	GCA	TCA Ser	ASD	Ala	AAA Lvs	Ala	Tyr	GAT Asp	Ser	Glu	, ,
Tari bili in			15	1.1.	· · ' · · · '			20			* E.T. S	·11.74	25	
	GCA Ala	CAT	AAT Asn	GTT Val	TGG	GCC Ala	ACA Thr	His	Ala	Cys	GTA Val	Pro	Thr	.14
65		:- -			30		_			35				

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GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
      Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
                                45
      GAA AAT TIT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
      Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
      ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231 Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
       65
                            70
      AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
      Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
                                    85
      AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
      Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
                        95
                                           100
      ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
      Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
          105
      ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
      Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
                   120
                                       125
      CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
      Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
                           135
      AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
      Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
                                   150
      ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
      Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
30
                      1.60
                                            165
      CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
      Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
          170
                               175
      AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
      Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
                  185
                                       190
      ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
      Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
                           200
                                               205
40
      CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
      Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
             210
                                                       220
                                   215
      GCA GAA GAA GAC ATA GTA ATT AGA TOO GCC AAT CTC ACA 699
      Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
                      225
                                            230
      GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
      Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
         235
                               240
      GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777 Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
                  250
                                       255
      AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT GCA 816
      Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
                          265
      ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
      Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
              275
                                   280
      AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
      Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
                      290
                                           295
      ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
      Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
                             305
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GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
      Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
                  315
      ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
      Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
                          330
      325
      AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
      Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
                                                       350
                                   345
              340
      GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
10
      Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
                                           360
                      355
      CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
      Pro Cys Arg Ile Arg Gin Ile Ile Asn Met Trp Gin Lys
                               370
15
          365
      ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167.
Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
                   380
                                       385
      ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
      Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
20
                                              .. 400:
                           395
      390
      AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
      Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
                                   410
               405
      ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
25
      Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp 420 425
      Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
                               435
3:0
          430
       CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
       Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
                                       450
                   445
      GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
      Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
35
                           460
                                               465
       TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
       Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
                                  475
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In addition to the listing in Table 1, Figure 3 shows the alignment of the amino acid sequences of the clones of each of the seven isolates. Corresponding residues from various clones are in boxes. In the figure, the amino acid sequences are aligned against MN-rgp120 (SEQ. ID. NO. 29).

In one embodiment, a gp120 polypeptide of this invention has the same amino acid sequence as the sequence of one of the breakthrough isolates. In another embodiment, the amino acid sequence is truncated, as described in detail hereinafter. In another embodiment, a gp120 polypeptide sequence of this invention contains a substitution, insertion, or

deletion (alteration) of one or more amino acids in the sequence of a breakthrough isolate. Usually, with the exception of amino acids that are not present in a truncated amino acid sequence and eliminate an epitope, a gp120 polypeptide of this invention will include alterations in the amino acid sequence of a breakthrough isolate that do not alter the polypeptide's ability to induce the same neutralizing antibodies as the amino acid sequence of the isolate.

In general, substitutions in the amino acid sequence of a gp120 polypeptide of this invention are conservative substitutions, particularly for amino acid residues in the V2, V3, and C4 domains of gp120, which domains contain neutralizing epitopes. However, non-conservative substitutions, particularly in domains that do not contain neutralizing epitopes are contemplated.

Conservative substitutions replace an amino acid with an amino acid of similar size and character. For example, a hydrophobic residue or hydrophilic residue is replaced with another hydrophobic residue or hydrophilic residue, respectively. Amino acids can be divided into the following groups: positively charged residues (K, R and H); negatively charged residues (D and E); amides (N and Q); aromatics (F, Y, and W); hydrophobics (P, G, A, V, L, I, and M); and uncharged residues (S and T). Usually, residues within a group are replaced with another member of the group.

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In one embodiment, critical amino acid residues in the V2, V3, and C4 domains of gp120 are identical to the corresponding residues in a breakthrough isolate sequence. Critical amino acid residues in the V2, V3, and C4 domains of gp120 are described in the experimental section. In another embodiment, all amino

acid residues in the V2, V3, and C4 domains of gp120 are identical to corresponding residues in a breakthrough isolate sequence.

5 Oligonucleotide Encoding gp120 from Breakthrough Isolates

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The present invention also provides novel oligonucleotides encoding gp120 from the breakthrough isolates which can be used to express gp120. An oligonucleotide of this invention encodes a polypeptide of this invention. The oligonucleotide can be DNA or RNA, usually DNA. Although numerous nucleotide sequences can encode the same amino acid sequence due to the degeneracy of the genetic code, conveniently, the oligonucleotides of this invention include a nucleotide sequence of a breakthrough isolate as illustrated in Table 1 (Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28). Usually, an oligonucleotide of this invention is less than about 5 kilobases (kb), preferably less than about 3 kb.

To express the encoded amino acid sequence, the oligonucleotide can be inserted into a transcription unit. The transcription unit can be inserted into a plasmid for production of cell lines, inserted into a virus (e.g.; vaccinia) or can be used directly as a DNA vaccine. Suitable transcription units for production of vaccine proteins are well known. A preferred expression vector, designated psvI6B5, is illustrated in Sequence ID No. 32. The vector includes an HSV-1 gD1 signal sequence joined to a linker sequence. The gp120 nucleotide sequence to be expressed starts with the Kpn I site of the gene. Since all gp120 or gp160 sequences contain this site, any gp120 nucleotide sequence can be analogously inserted into the vector and expressed. The vector ends with a polyA tail from SV40.

In addition to being useful to express a polypeptide sequence of this invention, the oligonucleotides of this invention can also be used in diagnostics to detect HIV isolates. For example, the oligonucleotide or a portion thereof encoding a neutralizing epitope can be used in branched chain DNA diagnostics or as a probe in in situ hybridization studies.

10 <u>Vaccine preparation</u>

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A gp120 polypeptide of this invention from a selected breakthrough isolate(s) in a suitable carrier is used to make a subunit vaccine. The polypeptide can be used alone, but is generally administered in a multivalent subunit vaccine that includes gp120 MN. In addition to one or more gp120 polypeptides of this invention, the vaccine generally includes the MN polypeptide (hereinafter, MN-rgp120). The vaccine usually includes about 3 to about 5 different gp120 polypeptides, but 30 or more different gp120 polypeptides can be used.

Preparation of gp120 polypeptides for use in a vaccine is well known and is described hereinafter. With the exception of the use of the selected HIV isolate, the gp120 subunit vaccine prepared in the method does not differ from gp120 subunit vaccines of the prior art.

As with prior art gp120 subunit vaccines, gp120 at the desired degree of purity and at a sufficient concentration to induce antibody formation is mixed with a physiologically acceptable carrier. A physiologically acceptable carrier is nontoxic to a recipient at the dosage and concentration employed in the vaccine. Generally, the vaccine is formulated for injection, usually intramuscular or subcutaneous injection. Suitable carriers for injection include

sterile water, but preferably are physiologic salt solutions, such as normal saline or buffered salt solutions such as phosphate-buffered saline or ringer's lactate. The vaccine generally contains an adjuvant. Useful adjuvants include QS21 (Quillaja saponaria, commercially available from Cambridge Biotech, Worcester, MA), which stimulates cytotoxic T-cells, and alum (aluminum hydroxide adjuvant). Formulations with different adjuvants which enhance cellular or local immunity can also be used. In particular, immunopotentiators such as cytokines can be included in the vaccine. Examples of suitable immunopotentiating cytokines include interleukins, such as interleukin-2 (IL-2) and interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-a). 15

Additional excipients that can be present in the vaccine include low molecular weight polypeptides (less than about 10 residues), proteins, amino acids, carbohydrates including glucose or dextrans, chelating agents such as EDTA, and other excipients that stabilize the protein or inhibit growth of microorganisms.

The vaccine can also contain other HIV proteins. In particular, gp41 or the extracellular portion of gp41 or HIV-1 core proteins such as P24, P17, and P55 can be present in the vaccine. Although the amino acid sequence of gp41 is more conserved than that of gp120, gp41 contains neutralizing epitopes. Preferably, any gp41 present in the vaccine is from an HIV isolate present in the vaccine. gp160 from an isolate used in the vaccine can replace gp120 in the vaccine or be used together with gp120 from the isolate. Alternatively, gp160 from a different isolate than those in the vaccine can additionally be present in the vaccine.

Vaccines according to the invention can also contain one or more soluble gp120 polypeptide

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sequences, or fragments thereof, in combination with an engineered virus specifically designed to express proteins that induce a cytotoxic T-cell response. Suitable engineered viruses are derived from, for example, Canary Pox virus, vaccinia viruses, attenuated human herpes viruses (such as, e.g., herpes simplex viruses), and Varicella Zoster. Exemplary engineered viruses are modified to express any HIV protein capable of inducing a cytotoxic T-cell response, such as those described above. Typically, immunization with the gp120/engineered virus vaccine is followed by administration of one or more doses of the gp120 polypeptide sequence(s) to boost the immune response. If desired, viruses can be engineered to express one or more gp120 polypeptide sequences of the invention, or fragments thereof, and used in vaccines with or without soluble gp120 polypeptide sequences.

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Vaccine formulations generally include a total of about 300 to 600 µg of gp120, conveniently in about 1.0 ml of carrier. Preferred formulations include use of twice the weight of a gp120 polypeptide in twice as600 µg alum. However, formulations having smaller amounts (e.g.; 50 μ g per dose) are also used, generally with alum or other adjuvants. The amount of qp120 for any isolate present in the vaccine will vary depending on the immunogenicity of the gp120. For example, gp120 from some strains of HIV may be less immunogenic than gp120 from the MN strain (Sequence ID No. 29). strains having different immunogenicity are used in combination, empirical titration of the amount of each virus would be performed to determine the percent of the gp120 of each strain in the vaccine. For isolates having similar immunogenicity, approximately equal amounts of each isolate's gp120 would be present in the vaccine. For example, in a preferred embodiment, the vaccine includes gp120 from the MN and a strain of this

invention at concentrations of about 300 μ g per strain in about 1.0 ml of carrier. When the vaccine includes gp120 from about 30 isolates, about 10 to about 50 μ g can be used. Methods of determining the relative amount of an immunogenic protein in multivalent vaccines are well known and have been used, for example, to determine relative proportions of various isolates in multivalent polio vaccines.

The vaccines of this invention are administered in
the same manner as prior art HIV gp120 subunit
vaccines. In particular, the vaccines are generally
administered at 0, 1, and at 6, 8 or 12 months,
depending on the protocol. A preferred protocol
includes administration at 0, 1, 6, and 12 months.

Following the immunization procedure, annual or
bi-annual boosts can be administered. However, during
the immunization process and thereafter, neutralizing
antibody levels can be assayed and the protocol
adjusted accordingly.

The vaccine is administered to uninfected individuals. In addition, the vaccine can be administered to seropositive individuals to augment immune response to the virus, as with prior art HIV vaccines. It is also contemplated that DNA encoding the strains of gp120 for the vaccine can be administered in a suitable vehicle for expression in the host. In this way, gp120 can be produced in the infected host, eliminating the need for repeated immunizations. Preparation of gp120 expression vehicles is described hereinafter.

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Although the gp120 isolates described herein can be used as a vaccine as described above, the amino acid sequences can also be used alone or in combinations in the same type of formulation for use as an immunogen, to induce antibodies that recognize the isolate(s) present in the immunogen. Immunogens are formulated in

the same manner as vaccines and can include the same excipients, etc. Antibodies induced by the immunogens can be used in a diagnostic to detect the HIV strain in the immunogen or to affinity purify the strain.

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gp120 Polypeptide Sequences and Chemokine Receptors While CD4 is the primary cellular receptor for HIV-1, it is not sufficient for entry of HIV-1 into cells. Co-receptors required in conjunction with CD4 have been identified. These co-receptors are members of the chemokine receptor family of seven-transmembrane G-protein coupled receptors. The chemokine superfamily is subdivided into two groups based on the amino terminal cysteine spacing. The CXC chemokines are primarily involved in neutrophil-mediated inflammation. and the CC chemokines tend to be involved in chronic inflammation. At least five CC chemokine receptors, designated CC-CKR1-5 (also known in the art as CCR1-5), and at least four CXC chemokine receptors, designated CXC-CKR1-4 (also known as CXCR-1-4), have been identified.

CXC-CKR-4 (CXCR-4), which has also been called the alpha-chemokine receptor fusin, serves as an entry cofactor for T-cell-tropic HIV-1 strains. CC-CKR-5 (CC-R5), which has been called beta-chemokine receptor, together with its related family members, such as CC-CKR-2b and CC-CKR3, serve as entry cofactors for macrophage-tropic HIV-1 strains. T-cell-tropic strains can infect primary T-cells and T-cell lines, but not macrophages, whereas macrophage-tropic strains can infect macrophages and primary T-cells, but not T-cell lines. T-cell- and macrophage-tropic strains are discussed more fully in Deng et. al., Nature 381:661-666 (1996), which is hereby incorporated by reference in its entirety. Examples of T-cell-tropic strains include laboratory isolates, such as IIIB and MN.

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Macrophage-tropic strains include primary isolates, including but not limited to A244, GNE6, GNE8, and breakthrough viruses from vaccinees immunized with gp120-based vaccines. Dual-tropic strains can use both types of co-receptors, entering cells via CXC-CKR-4 or via one or more CC-CKR family members, preferably CC-CKR-5, CC-CKR-2b, or CC-CKR-3. While the present invention is not intended to be bound or limited by any one theory, the entry of T-cell tropic and macrophage-tropic HIV-1 strains is believed to provide a unifying explanation of the differences in cell tropism between viral strains, the resistance to HIV-1 infection by many CD4-transfected nonprimate cells, and the HIV-1-infection resistance of a portion of the human population.

Accordingly, in one embodiment is a vaccine containing (1) a first gp120 polypeptide sequence, or fragment thereof, from a macrophage-tropic HIV-1 strain and/or a second gp120 polypeptide sequence, or fragment thereof, from a T-cell tropic strain, in combination with (2) a breakthrough isolate HIV gp120 polypeptide sequence, or fragment thereof, from a vaccinee vaccinated with the first and/or second HIV gp120 polypeptide sequence. Preferably, the vaccine includes at least two gp120 polypeptide sequences that bind to different chemokine receptors. In one embodiment, the vaccine includes first and second gp120 polypeptide sequences that bind to different chemokine receptors. In addition, the breakthrough isolate gp120 polypeptide sequence can bind to a different chemokine receptor than the chemokine receptor(s) bound by either or both of the first and second gp120 polypeptide sequence(s).

A preferred T-cell tropic strain is a laboratory isolate, most preferably MN. Preferred macrophagetropic viruses for use in the invention are GNE6 and GNE8, which are representative of the breakthrough

viruses disclosed herein and differ from MN in that their gp120s induce the formation of antibodies that recognize the gp120 sequences (e.g., the V3 domain) involved in binding to CC chemokine receptors, such as CXC-CKR-5.

In one embodiment, HIV infection is prevented by administering one or more chemokine receptor-binding gp120 polypeptide sequences, or fragment(s) thereof containing appropriate chemokine receptor-binding domains, in a vaccine, such as those described above. Preferably, the vaccine also includes one or more CD4-binding gp120 polypeptide sequences or appropriate fragments thereof. Such vaccines induce anti-HIV antibodies that inhibit viral gp120-chemokine receptor or -CD4 binding. In addition, such gp120 polypeptides can directly inhibit HIV infection by binding to one or more co-receptors for HIV infection, such as CD4 or a chemokine receptor, thus providing a prophylactic or therapeutic effect in treating HIV infection.

Preferably, gp120 polypeptide sequences useful in this

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Preferably, gp120 polypeptide sequences useful in this regard contain the T-cell binding (TCB) domain.

Various uses of chemokine receptor-binding gp120 polypeptides are discussed below with regard to the CC chemokine receptor family. However, those skilled in the art recognize that this discussion applies equally to CXC chemokine receptors that act as cofactors in HIV infection.

The gp120 polypeptides can be used as a composition containing one or more gp120 polypeptides, as described for use as a vaccine or immunogen. The composition can be administered, prophylactically or therapeutically, to a patient at risk of infection or in need of such treatment using the dosages and routes and means of administration described herein. However, chronic administration may be preferred and dosages can be adjusted accordingly. It is noted that in vivo

administration can also induce antibodies that bind viral gp120, further inhibiting virus binding to CC-CKR.

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The gp120 polypeptides can also be used in screening assays to identify antagonists of CC-CKR. For example, candidate antagonists can be screened for inhibition of binding of gp120 to a CC-CKR CC-CKR receptor that is isolated and attached to a surface (e.g., plastic dish) or recombinantly or naturally expressed on the surface of a cell. Antagonists can either bind gp120 or bind receptor. Preferred candidate antagonists include gp120 compounds, small gp120 peptides (5 to 20 amino acids in length, preferably 7 to 10 amino acids in length) or peptidomimetics of gp120 that bind receptor, monoclonal antibodies that bind gp120, and small organic molecules that bind either gp120 or receptor.

The antibodies induced by the gp120 polypeptides can also be used to induce anti-idiotype antibodies that bind CC chemokines. These anti-idiotype antibodies can be screened for binding to an anti-gp120 polypeptide antibody and inhibiting gp120 from binding CC-CKR receptor. Such anti-idiotype antibodies mimic gp120 by binding to CC-CKR receptor. Such antibodies, preferably human antibodies, can be obtained in a number of ways, such as human antibodies from combinatorial libraries (e.g., Burton et al. Adv. Immunolo. (1994) 57:191-280). It is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line

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immunoglobulin gene array in such germ-line mutant mice results in the production of human antibodies upon antigen challenge as described in Jakobovitis et al., Proc. Natl. Acad. Sci. USA 90: 2551 (1993); Jakobovits et al., Nature 362:255-258 (1993); Bruggermann et al., Year in Immuno. 7: 33 (1993).

Alternatively, phage display technology as described by McCafferty et al., Nature 348:552-553 (1990) can be used to produce human antibodies and 10 antibody fragments in vitro from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are closed in-frame either into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody 15 fragments on the surface of the phage particle. Because the filamentous particle contains a singlestranded DNA copy of the phage genome, selections based on the functional properties of the antibody also 20 result in selection of the gene encoding the antibody exhibiting those properties. Phage display can be performed in a variety of formats as reviewed by, for example, Johnson, et al., Current Opinion in Structural Biology 3:564-571 (1993).

25 Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352: 624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. 30 repertoire of V genes from unimmunized human donors (or embryonic cells) can be constructed. It has been demonstrated that antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol., 222: 581-597 (1991), or Griffith

et al., EMBO J., 12: 725-734 (1993).

In a natural immune response, antibody genes accumulate mutations at a high rate (somatic hypermutation). Some of the changes introduced confer higher affinity, and B cells displaying high-affinity surface immunoglobulin are preferentially replicated and differentiated during subsequent antigen challenge. This natural process can be mimicked by employing the technique known as "chain shuffling" (Marks et al., Bio/Technol. 10:779-783 [1992]). In this method, the affinity of "primary" human antibodies obtained by 10 phage display can be improved by sequentially replacing the heavy and light chain V region genes with repertoires of naturally occurring variants (repertoires) of V domain genes obtained from unimmunized donors. This technique allows the 15 production of antibodies and antibody fragments with affinities in the nM range. A strategy for making very large phage antibody repertoires has been described by Waterhouse et al., Nucl. Acids Res., 21: 2265-2266 (1993).20

Accordingly, antibodies that bind CC-CKR can be obtained by screening antibodies or fragments thereof expressed on the surface of bacteriophage in combinatorial lfbraries or in other systems as described above with a gp120 monoclonal antibody that inhibits gp120 binding to receptor.

In addition to screening antibodies with a gp-120 antibody, random or combinatorial peptide libraries can be screened with either a gp120 antibody or the gp120 compounds of the invention. Approaches are available for identifying peptide ligands from libraries that comprise large collections of peptides, ranging from 1 million to 1 billion difference sequences, which can be screened using monoclonal antibodies or target molecules. The power of this technology stems from the chemical diversity of the amino acids coupled with the

large number of sequences in a library. See for example, Scott et al., Cur. Open. Biotechnol. 5(1):40-8 (1994); Kenan et al. Trends Biochem. Sci. (1994) 19(2):57-64. Accordingly, the monoclonal antibodies, preferably human monoclonals or fragments thereof, generated as discussed herein, find use in treatment by inhibiting or treating HIV infection or disease progression, as well as in screening assays to identify additional pharmaceuticals.

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Production of qp120

gp120 for a vaccine can be produced by any suitable means, as with prior art HIV gp120 subunit vaccines. Recombinantly-produced or chemically synthesized gp120 is preferable to gp120 isolated directly from HIV for safety reasons. Methods for recombinant production of gp120 are described below.

Oligonucleotides encoding gp120 from breakthrough isolates and capable of expressing gp120 can be prepared by conventional means. For example, the nucleotide sequence can be synthesized. Alternatively, another HIV nucleotide sequence encoding gp120 can be used as a backbone and altered at any differing residues as by site-directed mutagenesis.

Site-directed mutagenesis is described in Kunkel et al, Proc. Natl. Acad. Sci. (USA) 82:488-492 (1985) and Zoller et al, Nuc. Acids Res. 10:6487-6500 (1982) and is well known.

In a preferred embodiment, the nucleotide sequence
is present in an expression construct containing DNA
encoding gp120 under the transcriptional and
translational control of a promoter for expression of
the encoded protein. The promoter can be a eukaryotic
promoter for expression in a mammalian cell. In cases
where one wishes to expand the promoter or produce
gp120 in a prokaryotic host, the promoter can be a

prokaryotic promoter. Usually a strong promoter is employed to provide high-level transcription and expression.

The expression construct can be part of a vector capable of stable extrachromosomal maintenance in an appropriate cellular host or may be integrated into host genomes. Normally, markers are provided with the expression construct which allow for selection of a host containing the construct. The marker can be on the same or a different DNA molecule, desirably, the same DNA molecule.

The expression construct can be joined to a replication system recognized by the intended host cell. Various replication systems include viral replication systems such as those from retroviruses, simian virus, bovine papilloma virus, or the like. In addition, the construct may be joined to an amplifiable gene, e.g. the DHFR gene, so that multiple copies of the gp120 DNA can be made. Introduction of the construct into the host will vary depending on the construct and can be achieved by any convenient means. A wide variety of prokaryotic and eukaryotic hosts can be employed for expression of the proteins.

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preferably, the gp120 is expressed in mammalian cells that provide the same glycosylation and disulfide bonds as in native gp120. Expression of gp120 and fragments of gp120 in mammalian cells as fusion proteins incorporating N-terminal sequences of Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (gD-1) is described in Lasky, L. A. et al., 1986 (Neutralization of the AIDS retrovirus by antibodies to a recombinant envelope glycoprotein) Science 233: 209-212 and Haffar, O.K. et al., 1991 (The cytoplasmic tail of HIV-1 gp160 contains regions that associate with cellular membranes.) Virol. 180:439-441, respectively. A preferred method for expressing gp120 is described in

the examples. In the examples, a heterologous signal sequence was used for convenient expression of the protein. However, the protein can also be expressed using the native signal sequence.

An isolated, purified gp120 polypeptide having one of the amino acid sequences illustrated in Table 1 can be produced by conventional methods. For example, the proteins can be chemically synthesized. In a preferred embodiment, the proteins are expressed in mammalian cells using an expression construct of this invention. The expressed proteins can be purified by conventional means. A preferred purification procedure is described in the examples.

qp120 Fragments 15

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The present invention also provides qp120 fragments that are suitable for use in inducing antibodies for use in a vaccine formulation. truncated gp120 sequence, as used herein, is a fragment 20 of gp120 that is free from a portion of the intact gp120 sequence beginning at either the amino or carboxy terminus of gp120. A truncated gp120 sequence of this invention is free from the C5 domain. The C5 domain of gp120 is a major immunogenic site of the molecule. However, antibodies to the region do not neutralize virus. Therefore, elimination of this portion of gp120 from immunogens used to induce antibodies for serotyping is advantageous.

In another embodiment, the truncated gp120 sequence is additionally free from the carboxy terminal region through about amino acid residue 453 of the gp120 V5 domain. The portion of the V5 domain remaining in the sequence provides a convenient restriction site for preparation of expression constructs. However, a truncated gp120 sequence that is free from the entire gp120 V5 domain is also

suitable for use in inducing antibodies.

In addition, portions of the amino terminus of gp120 can also be eliminated from the truncated gp120 sequence. In particular, the truncated gp120 sequence can be free from the gp120 signal sequence. The truncated gp120 sequence can be free from the carboxy terminus through amino acid residue 111 of the qp120 C1 domain, eliminating most of the C1 domain but preserving a convenient restriction site. However, the portion of the C1 domain through the V2 cysteine residue that forms a disulfide bond can additionally be removed, so that the truncated gp120 sequence is free from the carboxy terminus through amino acid residue 117 of the gp120 C1 domain. In a preferred embodiment, the truncated gp120 sequence is free from the amino terminus of gp120 through residue 111 of the C1 domain and residue 453 through the carboxy terminus of gp120.

The truncated gp120 sequences can be produced by recombinant engineering, as described previously. Conveniently, DNA encoding the truncated gp120 sequence is joined to a heterologous DNA sequence encoding a signal sequence.

It is understood that the application of the teachings of the present invention to a specific problem or situation is within the capabilities of one having ordinary skill in the art in light of the teachings contained herein. Examples of the products of the present invention and representative processes for their isolation, use, and manufacture appear below, but should not be construed to limit the invention. All literature citations herein are expressly incorporated by reference.

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EXAMPLES Materials and Methods

specimen collection from human volunteers. Blood was collected from MN-rgp120-immunized individuals who were infected with HIV-1 while participating in Phase I (NIH Protocol AVEG 016) and Phase II (NIH Protocol AVEG 201) HIV-1 vaccine trials sponsored by the National Institutes of Health (NIH). The demographics of the subjects in the study, and the study design have been described in McElrath; Seminars in Cancer Biol. 6:1-11 (1995); McElrath et al.; Abstracts from Eighth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS. Bethseda, MD 216 (1996). Specimens were obtained according to an informed consent protocol approved by the institutional review boards of the participating institutions. experimental section, the time of HIV-1 infection is 15 specified with regard to data provided by the NIH AIDS Vaccine Evaluation Network where PCR (RNA) and/or serologic assays were used to detect HIV-1 infection.

Sample preparation for cloning HIV-1 envelope 20 glycoproteins. Peripheral blood mononuclear cells (PBMCs) from HIV-1 infected vaccinees were prepared from heparinized venous blood by FICOLL-HYPAQUE gradient centrifugation. Cell number and viability were determined. After separation, PBMCs were washed 25 twice in phosphate-buffered saline and suspended at a cell density of 6x10" cells/ml in PCR lysis buffer (50 mM KCl, 10 mM Tris (pH 8.4), 2.5 mM MgCl₂, 0.1 mg/ml gelatin (Sigma), 0.45% NONIDET P40 detergent, 0.45% TWEEN 20 detergent (both detergents are commercially available from United States Biochemical Corp.) and 0.06 mg/ml Proteinase K (Gibco BRL) to lyse the cells. The lysate was incubated at 50-60°C for 1 hour, followed by inactivation of the Proteinase K at 95°C for 10 minutes. Lysates were shipped frozen and stored at -70°C until use.

Polymerase chain reaction (PCR) amplification.

Samples were subjected to two rounds of PCR amplification using the nested primers described below. In the first round, 25 μl aliquots of PBMC lysates (containing about 1 μg genomic DNA) were mixed with an equal volume of a PCR reaction mix containing 400 μM each dNTP, 200 μg/ml BSA (Sigma Chemical Corporation, RIA grade) and about 100 pmoles of each primer in 50 mM KCl, 20 mM Tris (pH 8.4) and 3 mM MgCl,. After an initial 10 minute denaturation step at 95°C, 5 units of Taq polymerase (AMPLITAQ, Perkin Elmer Cetus) were added during an 55°C soak step, and samples were overlayed with mineral oil.

The PCR profile was as follows: 2 cycles having 1 minute at 55°C, 2.5 minutes at 72°C and 1 minute at 94°C, followed by 28 cycles with 30 seconds at 55°C, 2.5 minutes at 72°C and 45 seconds at 94°C, and an extension step at 72°C for 5 minutes.

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Aliquots of 10 µl from the first-round reactions were re-amplified with appropriate nested primers in a final reaction volume of 100 µl, using either the reagents and profile described above or the reagents and profile described in the PCR Optimizer Kit (Invitrogen.) PCR reaction products were purified using QTAQUICK-spin columns (Qiagen Inc.) The primer pair used in the first round was either 120.os.F (5'-gggaattcggatccAGAGCAGAAGACAGTGGCAATGA with homologous sequence at position 6248-6270 of HIVPV22) (SEQ. ID. NO. 34) or JM11A

(5'-ctcgag-CTCCTGAAGACAGTCAGACTCATCAAG at position 6048-6074) (SEQ. ID. NO. 35) in the forward direction [Kusumi et al.; J. Virol. 66:875 (1992)] combined with 120.os.R (5'-ggtctagaagctttaGCCCATAGTGCTTCCTGCTGCT-CC at position 7836-7859) (SEQ. ID. NO. 36) in the reverse direction. The internal nested primers were 120.BX.F (5'-gggcggatcctcgaGGTACCTGTRTGGAAAGAAGCA at position

6389-6410; R: A or G) (SEQ. ID. NO. 37) and 120.is.R (5'-ggtctagaagctttaTGCTCCYAAGAACCCAAGGAACA at position 7819-7841; Y: T or C) (SEQ. ID. NO. 38). Heterologous primer sequences are shown in lower case letters.

Subcloning of PCR products and the expression of recombinant envelope glycoproteins as fusion proteins. The HIV-1 envelope glycoprotein gp120 sequences were cloned and expressed as chimeric genes and fusion proteins, where the signal sequence and 27 amino acids from the mature N terminus of herpes simplex virus type 1 (HSV-1) were fused to the N-terminal sequences of the gp120 genes, corresponding to amino acid 13 of the mature gp120 sequence. PCR products containing gp120 sequences from the breakthrough specimens were cloned into pRK5 expression plasmid as chimeric genes using combinations of restrictions sites engineered into the heterologous PCR primer tails and the Xho I site engineered into the N-terminal sequence of HSV-1 gD.

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The resulting double-stranded DNA was sequenced with Sequenase and the dGTP Reagent Kit (United States Biochemical Corp.). Sequences from glycoprotein D were provided to enhance expression and to provide a flag epitope to facilitate protein analysis, as described in Berman et al.; J. Virol. 7:4464-9 (1992); Nakamura et al.; AIDS and Human Retroviruses 8:1875-85 (1992); and Nakamura et al.; J. Virol. 67:6179-91 (1993).

Briefly, isolated DNA fragments generated by the PCR reaction were ligated into a plasmid (pRK.gD-5, pRKgDstop) designed to fuse the gp120 fragments, in frame, to the 5' sequences of the glycoprotein D (gD) gene of Type I Herpes Simplex Virus (gD-1) and the 3' end to translational stop codons. The fragment of the gD-1 gene encoded the signal sequence and 25 amino acids of the mature form of HSV-1 protein. To allow

for expression in mammalian cells, chimeric genes fragments were cloned into the pRK5 expression plasmid (Eaton et al., Biochemistry 291:8343-8347 (1986)) that contained a polylinker with cloning sites and translational stop codons located between a cytomegalovirus promotor and a simian virus 40 virus polyadenylation site.

The resulting plasmids were transfected into the 293s embryonic human kidney cell line (Graham et al., J. Gen. Virol. 36:59-77 (1977)) using a calcium phosphate technique (Graham et al., Virology 52:456-467 (1973)). Growth conditioned cell culture media was collected 48 hr after transfection, and the soluble proteins were detected by ELISA or by specific radioimmunoprecipitation where metabolically labeled 15 proteins from cell culture supernatants were resolved by sodium dodecyl sulfate polyacrylamide gel electrophoresis (PAGE) and visualized by autoradiography as described in Berman et al., J. Virol. 63:3489-3498 (1989) and Laemmli, Nature 20 227:680-685 (1970).

Serologic assays. Sera were assayed for antibodies to rgp120, antibodies to synthetic gp120 V3 domain peptides corresponding to sequences from the 25 gp120 V3 domain, and antibodies able to inhibit the binding of MN-rgp120 to cell surface CD4 using serologic assays described in Berman et al.; J. Virol. 7:4464-9 (1992); Nakamura et al.; AIDS and Human Retroviruses 8:1875-85 (1992); and Nakamura et al.; J. Virol. 67:6179-91 (1993). Endpoint titers of antibody binding to gp120 and V3 peptides were determined using three fold-serial dilutions of sera. The endpoint dilution titer was defined as the last dilution that produced an optical density value that 35 was two times higher than the mean of the optical

densities of 1:50 diluted, pooled, normal human sera. Antibody titers were calculated by a computer program that interpolated values between antibody dilutions. The inter-assay coefficient of variation of positive control standard sera was 35%.

Binding of monoclonal antibodies to rgp120 from breakthrough viruses. An ELISA similar to that described by Moore et al.; AIDS 3:155-63 (1989) was used to measure the binding of various monoclonal antibodies (MAbs) to rgp120s from breakthrough viruses. Briefly, Nunc-Immuno plates (Maxisorp, certified) were coated (100 µl at 5 µg/ml in PBS at 4°C overnight) with an affinity-purified sheep polyclonal antiserum to a 15 peptide at the C terminus of gp120 (D7324, International Enzymes, Fallbrook, CA). After washing once with PBS-0.05% TWEEN-20 detergent, the plates were blocked with PBS-1.0% BSA for 30-60 minutes at room temperature. Cell culture supernatants from 293s 20 cells, diluted to contain equivalent amounts of the gD-rgp120 fusion protein, were added and incubated for 2 hours at room temperature followed by three washes with PBS-0.05% TWEEN-20 detergent. Various MAbs were diluted in PBS-1.0% BSA and 100 μL of the diluted MAbs were added to each well and incubated for 1 hour at. room temperature.

The plates were washed 3 times and incubated with $100~\mu l$ of a horseradish peroxidase-conjugated second antibody (goat anti-mouse or anti-human IgG, Cappel) for 1 hour at room temperature. After 3 washes the plates were developed and the $OD_{\mu\nu}$, (optical density at 492 nm) read in a plate reader. Growth conditioned cell culture supernatants were normalized by dilution based on binding by MAb 5B6 which is specific for HSV-1 glycoprotein D fusion protein.

Virus neutralization assays. The ability of vaccinee sera to inhibit infection of MT4 cells by HIV-1_{MN} was measured in a cytopathicity assay where cell viability was quantitated using a calorimetric indicator dye, as described in Robertson et al.;

J. Virol. Methods 20:195-202 (1988). Briefly, a virus stock of HIV-1_{MN} (obtained from Dr. Michael Norcross, U.S. Food and Drug Administration) was prepared as the clarified supernatant from chronically infected H9/HIV-1_{MN} cell culture. H9 cells chronically infected with HIV-MN were pelleted and resuspended in one-tenth the original volume of medium. Cell-associated virus was released by the mechanical shearing effects of rapid vortexing of the cells as described in Wrin et al.; J. Virol. 69:39-48 (1995).

15 An amount of virus sufficient to ensure complete cell lysis killing in 7 days was incubated with three-fold serial dilutions of test antisera, and then used to challenge MT4 T-lymphoid cells in 10% FCS/RPMI-1640 cell culture media. The cultures were 20 incubated for 7 days at 37°C in 5% CO2, and then cell viability was tested by the dye MTT, as described by Robertson et al.; J. Virol. Methods 20:195-202 (1988). Virus neutralization endpoints were quantitated by measurement of OD at 570-650 nm, and then the endpoint 25 titers were calculated as the reciprocal of the antiserum dilution giving a signal that was two-fold above the control signal with unprotected (killed) cells. These titers were typically twice those calculated at 50% protection. 30

Results

Immunization history of infected subjects. Since 1992, 499 adults have been immunized with MN-rgp120 in Phase I trials in low or moderate risk individuals and in a Phase II clinical trial involving moderate to high

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risk individuals. The studies described herein entail the genetic and immunologic characterization of the first seven of nine individuals who became infected with HIV-1 through high risk behavior during the course of these trials. A listing of the trials and summary of the status of the vaccinees is presented in Table 2A. A listing of the analysis of the vaccinees is presented in Table 2B.

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TABLE 2A

Description of Vaccinees Infected with HIV-1

After Immunization with MN-rgp120

				#Antigen dose/
<u>s</u>	Study No.	Case No.	*Risk Group	<u>Adjuvant</u>
15	016	C6	M/H	300/QS21
	016	C8	М/Н	600/QS21
	016	C15	M/H	300/QS21
	201	C 7	м/н	600/Alum
	201	C11	M/H	600/Alum
20	201	C10	M/IDU	600/Alum
	201	C17	M/IDU	600/Alum

^{* -} M/H indicates male homosexual; M/IDU indicate male intravenous drug user.

^{† -} numbers indicate dose in micrograms of MN-rgp120 injected per immunization; QS21 indicates antigen was formulated in QS21 adjuvant; Alum indicates MN-rgp120 formulated in aluminum hydroxide.

TABLE 2B

Description of Vaccin es Infected with HIV-1

After Immunization with MN-rgp120

	Injection	Injections	Time of	pInterval:
Case	Schedule	before	HIV-1+	to HIV-1+
No.	(months)	<u> HIV-1+</u>	(months)	(months)
C6	0,1,10.5	2	4.00	2.00
C8	0,1	2	4.00	3.00
C15	0,1,2	or in the second of the second	6.25	4.00
C 7	0,1,6,12	3 3 3	9.25	3.00
C11	0,1,6,12	4	19.50	6.75
C10	0,1,6,19	* 3	19.50	13.50
C17	0,1,6,18	4	24.75	6.25

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n = indicates interval between last immunization and detection of HIV-1 infection.

Three of the infections occurred in a Phase I trial (NIH Protocol AVEG 201) that compared the safety and immunogenicity of MN-rgp120 formulated in two different adjuvants (alum and OS21), and four of the infections occurred in a Phase II trial aimed at establishing the safety and immunogenicity of MN-rgp120 in various high risk groups (e.g., intravenous drug users, homosexual and bisexual males, and partners of HIV-1 infected individuals).

Of the seven infections studied (Table 3), two (C6 and C8) occurred after two injections, three (C7, C10 and C15) occurred after three injections, and two (C11 and C17) occurred after receiving the four scheduled injections. The interval between receiving the last immunization and becoming infected was 2 to 13.5 months.

TABLE 3

P ak P st Boost MN-rgp120 Antibody Titers

in Vaccinees that Became Infected with HIV-1

granitation in Little Car	7.74	* * * * * * * * * * * * * * * * * * * *	•			
5 <u>Injections</u>	<u>C6</u>	<u>C8</u>	<u>C15</u>	<u>C7</u>	<u>C11</u>	C17
	• • • • •			‡ .		.ii
	<50	2185	79	<50	1890 na	na
2	21539	10125	na	413	32696 7771	7056
u later i jinglegli lesa et et j Tirk kulli lisari i e			• •			
3	#	#	4460	9707	34728 11627	1841
		*	· · · · · · · · · · · · · · · · · · ·		en de la companya de La companya de la co	3
4	#	#	#	#	r () ie e Helie e (e (eile e r e e (eile)	1134
					y diamentari da 75 da	1134

- indicates specimen not analyzed because of HIV-1 infection.

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na - indicates the sample was not available for testing.

boldface - indicates unusually low antibody titers.

Antibody response to gp120 in vaccinated individuals. The magnitude and specificity of the antibody response to MN-rgp120 was measured by ELISA in all infected individuals throughout the course of the immunization regime (Figure 1). Five of the seven

subjects exhibited normal antibody response kinetics that included a small but reproducible primary response (1:100-1:2,000) and a strong secondary (booster) response (titters ranging from 1:7,000-1:32,000), and antibody responses following third and fourth injections that were similar or marginally higher than those achieved after the second immunization (Figure 1, Table 3).

The antibody response observed in C7 (Figure 1C) was unusual in that no antibodies were detectable after the primary injection and a titer of only 1:350 was detected after the second injection. It thus appeared that C7 did not respond to the primary immunization, and that the antibody response obtained after the second injection represented a primary immune response. Consistent with this hypothesis, the third injection elicited a titer of only 1:9,707, typical of those normally seen after two immunizations.

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An atypical antibody response was also seen in subject C15 (Figure 1G) who was immunized according to 20 an accelerated immunization schedule of 0, 1, and 2 months. As expected, the antibody titer seen in this subject (1:4,460) was at the low end of what is typically achieved after two immunizations and was far below normal values for three immunizations. 25. of an effective booster response after the third immunization of C15 was not surprising in view of previous studies where an accelerated 0, 1, and 2 month immunization schedule in baboons [Anderson et al.; J. Infect. Dis. 160:960-9 ((1989)) similarly prolonged 30 the secondary response and failed to elicit an effective tertiary booster response.

Retrospective analysis of serum and plasma from subjects C6 (Figure 1A) and C8 (Figure 1B) indicated that they became infected with HIV-1 at some point between the second and third immunizations. Serologic

evidence of HIV-1 infection was evident in the gp120 antibody assays where the titers failed to decline two weeks after the second injection and instead formed an uncharacteristic high titer plateau (Figures 1A and 1B). A similar plateau in MN-rgp120 titer after the third injection, suggested that subject C7 became infected around week 36, approximately 16 weeks after receiving the third injection (Figure 1C). Subjects C10 (Figure 1E), C11 (Figure 1D), C15 (Figure 1G), and C17 (Figure 1F) developed unexpected increases in gp120 titers, typical of HIV-1 infection, after either the third or fourth immunizations. The data obtained demonstrate that immunologic priming for MN-rgp120 antibody responses is insufficient to provide universal protection from HIV-1 infection.

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Antibody titers to the V3 domain. To further characterize the antibody response to gp120, antibody titers were measured to a synthetic V3 domain peptide 20 of MN-rgp120 containing the principal neutralizing determinant (PND). Five of the seven subjects developed good V3 titers (1:400 to 1:4000) after the second immunization, however two subjects (C7 and C15) required three immunizations before developing 25 significant tiers (Figures 1C and 1G). As had been observed previously (11), the peak V3 titers in some individuals (e.g. C11, C10, C17) appeared to decline with each successive immunization (Figures 1D, 1E, and After HIV-1 infection, two patterns of V3 reactivity were observed. Three subjects (C6, C7, and C10) showed large increases in titer to V3 domain peptides (Figures 1A, 1C, and 1E) whereas C8 (Figure 1B) showed a large decrease in V3 titer. the time of analysis, the data were insufficient to

draw any conclusions regarding the changes in V3 titers in response to HIV-1 infection in subjects C11, C15 and C17.

The results obtained indicate that the ability to form antibodies reactive with the V3 domain at various time-points prior to HIV-1 infection is not a valid correlate of protective immunity against all strains of HIV-1.

10 CD4 Inhibition titers. Antibodies that block the binding of gp120 to CD4 represent a heterogeneous class of virus neutralizing antibodies. Some are known to bind to the C4 domain of gp120 [Nakamura et al.; J. Virol. 67:6179-91 (1993); Anderson et al.; J.

Infect. Dis. 160:960-9 ((1989)), and some are known to recognize conformation dependent discontinuous epitopes [Berman et al.; J. Virol. 7:4464-9 (1992);
Nakamura et al.; J. Virol. 67:6179-91 (1993);
McKeating et al.; AIDS Research and Human Retroviruses
8:451-9 (1992); Ho et al.; J. Virol. 65:489-93 (1991);
Barbas et al.; Proc. Natl. Acad. Sci. USA 91:3809-13

(1994)].

One way to detect antibodies to both types of
epitopes is to measure the ability of vaccinee sera to
prevent the binding of [12]-labeled gp120 to cell
surface CD4 [[Nakamura et al.; AIDS and Human
Retroviruses 81875-85 (1992); Nakamura et al.;
J. Virol. 67:6179-91 (1993)]. CD4 blocking titers were
detected in all seven of the vaccinees prior to
infection (Figure 2) with peak titers that ranged from
1:10-1:300. At the last time point prior to infection,
the CD4 titers in five of the seven vaccinees was low
(1:30 or less). One vaccinee (C17), however, possessed
a CD4 blocking titer of about 1:300 prior to infection
(Figure 2F). Thus, the lack of antibodies that block
the binding of MN-rgp120 to CD4 cannot account for all

of the infections. Large increases in CD4 blocking titers (1:100-1:1,000) were seen in five of the seven subjects after HIV-1 infection. These included vaccinees C6, C7, C8, C10, and C11. These results demonstrate that the CD4 blocking titers elicited by MN-rgp120 were lower than those elicited by natural infection.

Virus neutralizing activity. The virus

neutralizing activity of antisera from

MN-rgp120-immunized subjects was measured using a
colorimetric assay that measured the viability of MT-4
cells after incubation with antibody treated virus
(HIV-1_{MN}). Since the actual date of infection was not
known for any of the breakthrough infections, and serum
samples were collected infrequently, the magnitude of
the neutralizing antibody response at the time of
infection is not known for any of the vaccinees.

Of the seven infections examined, the serum sample closest to the time of infection was that obtained from C7, where a neutralizing titer of 1:15 to HIV-1_{MN} was present three weeks prior to detection of HIV-1 infection (Table 4). In all other cases, however, the interval between the last injection and the time of infection was 10 to 25 weeks.

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TABLE 4

Neutralization Activity of Sera from Vaccin es

Infected with HIV-1

F. F. S.	1911 1 . e.B.		In	rected v	MICU HI	(<u> </u>		**************************************
e salar oʻrgilir Hafi indi afala Diadi a firdilar Billar Makillar	<u>Week</u>	<u>C6</u>	<u>C8</u>	<u>C15</u>	<u>c7</u>	<u>C11</u>	<u>C10</u>	<u>C17</u>
				4104	~1.0°±	~1.O+	<10*	<10*
5	0			<10*	<10*	<10*	710 *	\10 "
	2	<10	<10	<10	- , , ,	_		
	4	<10*	<10*	nd*	<10*	<10*	<10*	<10*
	6	10	80	-	<10	30	150	150
	8	-		nd*	-	. -	· -	
10	10	<u>-</u>	<u>.</u>	35			· - .	
	15	· · · · · · · · · · · · · · · · · · ·		.	<10	- .	· -	-
*	16	150#	250#	· •	-	30	10,	<10
	24			150#	<10*	20*	<10*	<10*
	26				70	500	200	400
15	30				- ' ."		40	100
	33				15	- ,	-	
*.	35			*	-	100	-	
	36				30#	=	10	40
	52					30*	<10	<10
20	54				X	250	_	
	57					100	-	
	63				*	90	-	<u> </u>
	64			ļ. — — — — — — — — — — — — — — — — — — —		-	-	<10
	77					40#	<u>-</u>	. <u>-</u>
25	78			**			500#	10*
	80							100
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* - indicates immunization.

- indicates HIV-1 positive.

nd - indicates not done.

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3.5

- - indicates sample not available.

When sera from the two early infections were examined (Table 4), one individual (C6) had a peak 10 neutralizing titer of 1:10 ten weeks prior to detection of HIV-1 infection, whereas the other individual (C8) had a neutralizing titer of 1:80 ten weeks prior to detection of HIV-1 infection. Subject C15, who was 15. immunized according to an accelerated immunization schedule, developed a neutralizing titer of 1:35 after the third injection, 14 weeks prior to HIV-1 infection. Subject C10, who had a peak neutralizing titer of 1:200 following the third immunization (week 24), had no detectable titer at week 52, six months prior to the 20 first indication of HIV-1 infection (week 78).

Subject C11 possessed a neutralizing titer of 1:90 at fourteen weeks prior to detection of HIV-1 and a peak titer of 1:500 following the third immunization. Similarly vaccinee C17 had a neutralizing titer of 1:150 fourteen weeks prior to infection and a peak titer of 1:400 at two weeks after the third immunization.

Based on the rate of decay of the gp120 response of approximately two months [Belshe et al.; JAMA 272(6):475-80 (1994)], as well as the observation that neutralizing titers of 1:150 decayed to 1:10 in 10 weeks in vaccinees C10 and C17, it appears that neutralizing titers in C8, C15, C11, and C17 could have declined to 1:10 or less in the intervals between the last pre-infection serum sample and the time of HIV-1

detection.

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The results of these studies demonstrated that all vaccinees developed some level of virus-neutralizing antibodies at some time prior to HIV-1 infection, and that the magnitude of the neutralizing response was probably low at the time of infection. In general, the magnitude of the virus-neutralizing response observed in the individuals that became infected with HIV-1 was comparable to that seen in non-infected vaccinees as described in Belshe et al.; JAMA 272(6):475-80 (1994).

sequences of Viruses. To evaluate the similarity of the breakthrough viruses with the vaccine antigen, nucleotide sequences for gp120 from all seven breakthrough viruses were determined. Envelope glycoprotein genes were amplified from proviral DNA using the polymerase chain reaction. Sequences were obtained by direct amplification of DNA from lysates of gradient-purified lymphocytes obtained directly from patient blood without any intermediate tissue culture or amplification step.

A listing of the complete gp120 sequences (two clones per specimen) is provided in Figure 3. All seven envelope glycoproteins possessed sequences typical of subtype (clade) B viruses. The overall homology with MN-rgp120 ranged from 69-80% (Table 5).

TABLE 5

Comparison of MN-rgp120 Sequence with Sequenc s

from Infected Vaccinees*

		N C6.1	C8.3	C7.2	C11.5	C10.5	C17.1	C15.2
5	MN 1	00 79	78	70	75	69	80	72
	C6.1	100	78	70 ,	81	75	90	79
	C8.3		100	68	80	76	84	83
	C7.2	.: .:		100	80	73	76	73
	C11.5			. * .	100	75	70	80
10	C10.5			:		100	7.0.	72
	C17.1			, .	. •		100	87
	C15.2		· .					100

^{* =} Data indicate percent identity.

Interestingly, a high percentage (four of seven) of the breakthrough viruses differed from MN-rgp120 by 25-30% [Myers et al.; Retroviruses and AIDS Database, Los Alamos National Laboratory (1992 and 1995)].

Historically this degree of sequence variation is typical of inter-subtype (intra-clade) variation rather than intra-subtype variation which is expected to be in the 10-20% range [Myers et al.; Retroviruses and AIDS Database, Los Alamos National Laboratory (1992 and 19950]. Of the viruses with the greatest homology to MN-rgp120, two (C6 and C8) occurred as early infections, prior to complete immunization, and one (C17) occurred as a late infection.

Polymorphism in the V3 Domain. Of particular interest were polymorphisms in regions known to contain epitopes recognized by virus neutralizing antibodies. The best characterized neutralizing epitope, the principal neutralizing determinant (PND), occurs at the

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tip of the V3 loop. In subtype B viruses, approximately 60% possess the MN serotype-defining signature sequence, IGPGRAF (SEQ. ID. NO. 39), based on identity with the prototypic MN strain of HIV-1 [Berman et al.; J. Virol. 7:4464-9 (1992); Myers et al.; Retroviruses and AIDS Database, Los Alamos National Laboratory (1992 and 1995); La Rosa et al.; Science 249:932-5 (1990)].

Three of the viruses (C6, C8, and C17) possessed

the MN serotype signature sequence (Figure 3). In
contrast, four viruses possessed sequences with radical
amino acid substitutions in the PND [IGPGRAW (C7),
LGPGSTF (C11), IGPGRVL (C10), and IGPGSAF (C15)]
(SEQ. ID. NOS. 40-43, respectively), and therefore were
classified as "non-MN like" viruses. Of note, each of
the four "non-MN-like" sequences were rare (Table 6)
and were not typical of the most common "non-MN"
variants of subtype B viruses [Myers et al.;
Retroviruses and AIDS Database, Los Alamos National
Laboratory (1992 and 1995)].

TABLE 6
Frequency of Polym rphisms at the Principal
Neutralizing Determinant in HIV-1 Infected
Individuals Immunized with MN-rpp120*

5	V3 Sequer	nce	Observed		Dataset	Frequency	
	Sequence	<u>n</u>	Frequency	4.5	LANL (n=519)	LANL.1 (n=160)	•
	GPGRAF	3	0.42	0.67	0.57	0.66	0.60
	GPGRAW	1	0.14	0.03	0.013	0.06	0.010
10	GPGRVL	1	0.14	<0.02	0.004	<0.006	<0.008
	GPGSTF**	1	0.14	<0.02	<0.002	<0.006	<0.004
*	GPGSAF	1	0.14	0.02	0.011	<0.006	<0.004

- * Data set GNE refers to a collection of
 52 independent isolates collected in 1992;
 dataset LANL refers to a collection of
 519 sequences reported by Myers et al.,
 Retroviruses and AIDS Database, Los Alamos
 National Laboratory 1992 and 1995; LANL.1 refers
 to a collection of 160 epidemiologically unlinked
 individuals provided by B. Korber (personal
 communication); dataset La Rosa refers to sequence
 data reported by La Rosa et al., Science 249:932-5
 (1990).
 - ** Sequences were not present in the data sets examined.

The prevalence of viruses with PND sequences

30 matching the breakthrough viruses ranged from a high of
1.3% (C7) to a low of 0.2% (C11) in a listing of 519
subtype B sequences compiled by the Los Alamos National
Laboratory [Myers et al.; Retroviruses and AIDS
Database, Los Alamos National Laboratory (1992 and
1995)]. Similarly low frequencies were observed in

three other independently derived data sets (Table 6). The occurrence of these sequences did not differ significantly between data sets collected prior to 1985 [La Rosa et al.; Science 249:932-5 (1990)] and data collected 1992, or from a set of 160 epidemiologically unlinked individuals (B. Korber, personal communication). All four sets of data agreed that the prevalence of viruses with MN-like PND sequences was in the range of 60%. Based on this data, four of the seven breakthrough infections were determined to be caused by viruses that fell outside of the spectrum of viruses that the vaccine was expected to prevent.

Other features of breakthrough virus V3 domains.

Like MN-rgp120, the V3 domains of all of the breakthrough viruses were 36 amino acids in length. However, all seven viruses differed from MN-rgp120 with respect to the number of glycosylation sites and with respect to the syncytium-inducing (SI) signature sequence.

The sequence of MN-rgp120 is somewhat unusual [Myers et al.; Retroviruses and AIDS Database, Los Alamos National Laboratory (1992 and 1995)] in that it lacks an N-linked glycosylation site at position 306 in the V3 domain. The lack of this glycosylation site does not appear to be antigenically significant since antisera to MN-rgp120 are known to neutralize a variety of viruses (e.g. SF-2, DU6587-5, DU4489-5, CC) that possess a glycosylation site at this position [Berman et al.; J. Virol. 7:4464-9 (1992)]

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In addition, the V3 domain of MN-rgp120 possessed sequence polymorphisms (R at position 311, K at position 324, K at position 328) typical of syncytium inducing viruses [Fouchier et al.; J. Virol. 66:3183-87 (1992)], whereas all seven breakthrough viruses possessed sequences associated with non-syncytium-

inducing viruses. Syncytium-inducing viruses have been associated with rapid disease progression [Tersmette et al.; J. Virol. 62:2026-32 (1988)] and T cell tropism [O'Brien et al.; Nature (London) 348:69-73 (1990); Shioda et al.; Nature (London) 349:167-9 (1991)]. To date viruses with these properties have not been recovered from any of the MN-rgp120 immunized volunteers.

Previous investigations have identified additional neutralizing epitopes in the V1, V2 and C4 domains of gp120 [Nakamura et al.; J. Virol. 67:6179-91 (1993); McKeating et al.; AIDS Research and Human Retroviruses 8:451-9 (1992); Ho et al.; J. Virol. 65:489-93 (1991); Barbas et al.; Proc. Natl. Acad. Sci. USA 91:3809-13 (1994); McKeating et al.; J. Virol. 67:4932-44 (1993); Moore et al.; J. Virol. 67:6136-6151 (1993); Davis et al.; J. Gen. Virol. 74:2609-17 (1993)].

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The best characterized of these neutralizing epitopes is in the C4 domain which has attracted special attention because antibodies binding to this area are known to block the binding of gp120 to CD4 [Moore et al.; AIDS 3:155-63 (1989); McKeating et al.; AIDS Research and Human Retroviruses 8:451-9 (1992)]. Because the epitope is located in a conserved (C) domain, naturally-occurring polymorphism in this region is far more limited than in other neutralizing epitopes. Nakamura et al.; J. Virol. 67:6179-91 (1993) reported that the binding of a number of neutralizing MAbs was dependent on K at position 429.

Comparison of the sequence of MN-rgp120 with other strains of HIV-1 showed that a common polymorphism, involving the substitution of E for K, occurs at this position. Indeed, substrains of the same virus isolate often show polymorphism at this position. The HXB2

substrain of HIV-1_{IAI} contains K at position 429, whereas the BH10, IIIB, and LAV substrains of the HIV-1_{IAI} contain E at this position [Nakamura et al.; J. Virol. 67:6179-91 (1993)]. Similarly, the 1984 isolate of HIV-1_{MN} exhibited E at this position, while the 1990 isolate of HIV-1_{MN}, used to produce MN-rgp120, possessed K at this position.

When the sequences of the infected vaccine recipients were examined (Figure 3), the virus from subject C17, like MN-rgp120 contained K at position 429, whereas the six other viruses that differed from the vaccine immunogen possessed E at this position. These results demonstrated that six of the seven breakthrough viruses differed from the vaccine immunogen at the CD4-blocking, neutralizing epitope in the C4 domain of gp120.

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Studies with monoclonal antibodies have defined neutralizing epitopes in the V1 and V2 domains of gp120 [McKeating et al.; J. Virol. 67:4932-44 (1993); Moore et al.; J. Virol. 67:6136-6151 (1993); Davis et al.; J. Gen. Virol. 74:2609-17 (1993)]. Like the polymorphisms that occur in the C4 domain, the V2 domains exhibit several common polymorphisms that affect the binding of virus neutralizing antibodies. One such polymorphism occurs at position 171 which is critically important for the binding of murine MAb 1025, whereas residue 187 is important for the binding of MAb several MAbs represented by 1088.

When the V2 domain sequences were examined (Figure 3), all of the infected-vaccinee viruses differed from MN-rgp120 in that R replaced G at position 171 and I or V replaced E at position 187. Antibodies recognizing these adjacent sites in the V2 domain of MN-rgp120 would not be expected to neutralize viruses with radical amino acid substitutions at these position. Thus, all seven

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breakthrough viruses differed from MN-rgp120 at a neutralizing epitope in the V2 domain of gp120.

Other neutralizing epitopes have been reported in the V1 domain of qp120 [O'Brien et al.; Nature (London) 348:69-73 (1990); McKeating et al.; J. Virol. 67:4932-44 (1993)]. Although the neutralizing epitopes in the V1 domain of MN-rgp120 have not been characterized, the polymorphism seen among the breakthrough viruses in this region was interesting. Particularly striking (Figure 3) was that the length of 10 this domain ranged from 20 amino acids (C17) to 45 amino acids (C6), and the number of N-linked glycosylation sites ranged from 2 to 6. In contrast, the V1 domain of MN-rgp120 is 31 amino acids in length and encodes three N-linked glycosylation sites. 15

Although examination of sequence databases suggest that variation in the V2 region is comparable to the V1 region, the V2 region of the breakthrough viruses showed less variation than expected. Specifically, the length of the V2 region ranged from 36 amino acids (C7) to 39 amino acids in length, with six of seven viruses containing three N-linked glycosylation sites in this domain. A high degree of polymorphism was found in the V4 region where sequences ranged from 26 (C10) to 33 25 (C15, C7) amino acids in length and contained either 4 or 5 N-linked glycosylation sites.

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Antigenicity of envelope glycoproteins from breakthrough viruses. To determine the significance of sequence variation on glycoprotein antigenicity, recombinant gp120 was prepared from the viruses of all seven infected vaccinees (Figure 4). In these studies a series of MAbs was assembled and their binding to MN-rgp120 was compared to that of rgp120 from the vaccinee isolates by ELISA (Table 7).

TABLE 7

Relative Reactivity* of MAD Binding to rgp120 from Infect d Subjects Compared with Binding to MN-rgp120

			V3	Discor	tinuous	<u>C8</u>	<u>V2</u>
5	qp120	1034	<u>50.1</u>	<u>1.5E</u>	<u>1025</u>	1024	1088
	MN	1.0	1.00	1.00	1.00	1.00	1.00
	C6.1 C6.5	0.37 0.33	0.37 0.33	0.17 0.75	0.00	0.00	0.00
10	C8.3	0.11 0.14	0.37 0.34	0.38 0.29	0.00	0.00	0.00
	C7.2	0.47	0.60	0.71	0.00	0.00	0.00
	C11.5 C11.7	0.00	0.00	0.17 0.17	0.00	0.00	0.00
15	C10.5	0.33	0.40	0.46	0.24	0.03 0.07	0.04 0.09
	C17.1 C17.3	0.33 0.37	0.52 0.56	0.33	0.00	0.30 0.38	0.07 0.06
	C15.2 C15.3	0.00	0.47 0.37	0.92 0.63	0.00	0.00	0.00
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* - Relative reactivity values represent ratio of optical densities obtained with rgp120 from patient isolates divided by optical density obtained for MN-rgp120 at a MAb concentration of 2 micrograms per milliliter.

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In control experiments, the binding of MAb 5B6 (which is specific for the HSV gD-1 flag epitope fused to the N terminus of all of the rgp120 protein) was used to standardize the amount of gp120 from each isolate (Figure 5A). These studies demonstrated that the assay was carried out under conditions where equivalent amount of rgp120s were captured onto wells of microtiter plates.

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The antigenic structure of the V3 domain was examined using the 1034 MAb (isolated from mice immunized with MN-rgp120 as described in Nakamura et al.; J. Virol. 67:6179-91 (1993) and the 50.1 MAb (prepared from mice immunized with a synthetic V3 domain peptide as described in Rini et al.; Proc.

Natl. Acad. Sci. USA 90:6325-9 (1993). Both MAbs are known to exhibit potent virus neutralizing activity. When binding to the recombinant proteins was examined, the MAb binding to MN-rgp120 was at least 10-fold greater than to any of the breakthrough virus envelope proteins (Figure 5 B and C). Surprisingly, rgp120 from the three patient isolates (C8, C6, and C17) that possessed the MN serotype-defining sequence, IGPGRAF (SEQ. ID. No. 39), varied from one another in their MAb binding activity. Thus, the binding of MAb 1034 and MAb 50.1 to rgp120 from C17 was significantly greater than the binding to rgp120s from C6 and C8.

A distinction in the epitopes recognized by these MAbs was evident since C6-rgp120 and C8-rgp120 gave comparable binding with 50.1, whereas 1034 bound better to the C6-derived protein than the C8-derived protein. The poorest MAb reactivity was with rgp120s from C11 and C15. This result was consistent with sequence analysis demonstrating that these two viruses both possessed the radical substitution of S for R at position 18 in the V3 domain. Surprisingly, both of these MAbs exhibited better than expected binding to rgp120 from the C7 and C10 viruses. Like MN-rgp120, both proteins contained the penta-peptide, IGPGR sequence (SEQ. ID. NO. 44) in the V3 loop, but differed from MN-rgp120 in that V and L replaced A and F at positions 319 and 320 in gp120 from C10, and W replaced F at position 320 in gp120 from C7. These results indicate that R at position 318 is essential for the binding of these two MAbs, and that the epitopes recognized by 1034 and 50.1 are not completely destroyed by the hydrophobic substitutions at positions 319 and 320.

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As predicted from the sequence data, there was

little if any binding to the breakthrough virus rgp120s
using MAbs (1088 and 1025) directed to the V2 region of

MN-rgp120. Also consistent with sequence data was the observation that MAb 1024 directed to the C4 domain of MN-rgp120 gave some reactivity with C17-rgp120 which, like MN-rgp120 contained K at position 429, but gave no reactivity with the other isolates that contained E at residue 429.

Together, these studies demonstrated that the antigenic structure of all seven breakthrough viruses differed from the vaccine immunogen at three well characterized neutralizing epitopes.

A totally different pattern of reactivity was observed with the human hybridoma, MAb 15e, prepared from an HIV-1 infected individual as described in Ho et al.; J. Virol. 65:489-93 (1991). With this MAb, the greatest binding was achieved with MN-rgp120 and rgp120 from C7, and the poorest reactivity was seen with the two clones of rgp120 from the C11. Moderate, but comparable reactivity was seen with rgp120s from the C10 and C17.

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These results demonstrate that the 15e epitope is polymorphic, and that the epitope is conserved on MN-rgp120 and rgp120 from C7, but has been lost on Interestingly, the two different rgp120s from C11. clones of gp120 derived from C6 gave strikingly different patterns of antibody binding. Thus, rgp120 from clone C6.5 exhibited strong reactivity with this antibody, whereas rgp120 from clones C6.1 exhibited significantly weaker activity with this MAb. Comparison of sequence data (Figure 3) showed that the two C6 clones differed at 6 amino acid positions. Based on comparative binding to the other viral proteins of known sequence, it appeared that the substitution of K for I at position 351 in the C3 domain of gp120 could account for the difference in binding activity. This result is also consistent with both clones of C11 similarly containing a positively-

charged K at this position, and also being poorly reactive with this MAb. Alternatively, a T for I substitution at position 439 in the C4 domain could account for the difference in 15e binding between C6.1 and C6.5. Although the inability of the two C11 clones to bind 15e cannot be explained by polymorphism at this position in the C4 domain, they could be affected by the adjacent T for M substitution at position 434.

10 Discussion

In these studies, the viruses and immune responses in seven of nine vaccinees who became infected with HIV-1 through high risk activity while participating in Phase I or Phase 2 trials of MN-rgp120, a candidate HIV-1 vaccine were analyzed. Such infections would be expected to occur for one of two reasons: 1) lack of sufficient immune response at the time of infection; or 2) infection with viruses that fall outside of the antigenic spectrum expected to be covered by the vaccine immunogen. The data indicate that both explanations may be involved with the infections observed (Table 8).

TABLE 8
Summary of Breakthrough Infections

Homologous to MN-rap120

		MN-rgp120			
5 Case No	Adequate	Homology	V3	C4	V 2
	Immunization	(%)	PND	Epitope	<u>Epitope</u>
C6		79	ere el eramètatea esa. El como ≢en esa da co Como el como e	renge – 1916. Salas – Salas Salas	
С8		78		-	-
C15	<u> </u>	72		- E	_
C7	<u>-</u> 	70		- -	-
10 c11		75		-	
C10		69	n kona <u>n</u> maalii Tarkalii, ja	in in L e See tage de la company	÷
C17		80		.	· ·

Two of the infections occurred in individuals who 15 failed to receive the minimum three doses of vaccine typically required for the induction of protective immunity with protein subunit vaccines (e.g. hepatitis B virus formulated in alum adjuvant as described in Francis et al.; Ann. Int. Med. 97:362-6 (1982). 20 additional breakthrough infections occurred in vaccinees who had weak or undetectable primary (C7) and booster (C15) responses. Of the three individuals who became infected with HIV-1 after receiving three or more productive immunizations (C10, C11, and C17), at 25 least two, and possibly all three, appear to have become infected more than six months after receiving their last immunization. Because antibody titers to MN-rgp120 typically decay with a half-time of 2 to 2.5 months [Belshe et al.; JAMA 272(6):475-80 (1994); Berman et al.; AIDS 8:591-601 (1994)], antibody titers would be expected to have decayed at least eight-fold and possibly as much as sixty four-fold at the time of infection. Thus, the lack of a sufficient immune

response at the time of infection represents a potential explanation for at least six of the seven breakthrough infections.

Data from vaccine efficacy studies in gp160 immunized chimpanzees [McElrath et al.; Longitudinal Vaccine-Induced Immunity and Risk Behavior of Study Participants in AVEG Phase II Protocol 201. In: Abstracts from Eighth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS. Bethseda, MD 1996:216] challenged with HIV-1, and 10 gp120-immunized rhesus macaques challenged with a chimeric SIV/HIV-1 virus (SHIV) suggest that the magnitude of the neutralizing antibody response at the time of infection is a critical correlate of protective immunity. If maintaining neutralizing antibody titers proves to be a valid correlate of protective immunity in humans, then formulations (e.g. novel adjuvants) or immunization regimes (frequent boosting) designed to maximize the antibody responses may be required to achieve long lasting protection. Use of a booster 20 every six months may be advantageous.

The other likely explanation for the late infections is the antigenic difference between the vaccine and the breakthrough virus envelope glycoproteins. This explanation is supported by the observation that four of the seven breakthrough viruses possessed envelope glycoproteins that differed from the MN-rgp120 by 25-30% at the amino acid level. Differences of this magnitude have historically [Myers et al., Retroviruses and AIDS Database, Los Alamos National Laboratory (1992 and 1995)] been associated with inter-subtype variation and far exceeds the average 10-20% variation expected for viruses within the same subtype.

Although the biologic significance of sequence variation in many regions of the envelope glycoprotein

is unclear, polymorphism at neutralizing epitopes is an important factor that affects vaccine efficacy. Previous studies [Salmon-Ceron et al.; AIDS Res. and Human Retroviruses 11:1479-86 (1995); Javaherian et al.; Science 250:1590-3 (1990)] have demonstrated that the breadth of neutralizing activity that could be elicited by HIV-1 envelope derived vaccines was critically dependent on the sequence of epitopes in the V3 domain (e.g.; the PND). Thus, candidate vaccines based on the LAI strain of HIV-1 (the prototypic "non-MN-like" subtype B virus), exhibited little or no cross neutralizing activity with subtype B viruses, whereas vaccines that contained the "MN-like-" PND sequence (IGPGRAF) (SEQ. ID. NO. 44) exhibited broad cross neutralizing activity. That four of the seven breakthrough viruses possessed envelope glycoproteins with radical amino acid substitutions in the PND is consistent with the explanation that differences in antigenic structure explain some of these infections.

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Over the last few years, it has become clear that polymorphism among "MN-like" viruses occurs at neutralizing epitopes outside of the PND. The best example occurs in the C4 domain where two antigenically distinct variants are distinguished by the presence of either K or E at position 429 [Moore et al.; AIDS 3:155-63 (1989)]. Because six of the seven breakthrough viruses differed from the vaccine strain in that they contained E rather than K at position 429, antibodies raised to the C4 domain of MN-rgp120 were unlikely to neutralize the viruses infecting in six of the seven vaccinees.

Other neutralizing epitopes are known to be present in the V1 and V2 domains of gp120. Although these regions are highly variable, due to insertions and deletions, neutralizing epitopes have been described by McKeating et al.; J. Virol. 67:4932-44

(1993); Moore et al.; J. Virol. 67:6136-6151 (1993); and Davis et al.; J. Gen. Virol. 74:2609-17 (1993). Several of these epitopes overlap an amino terminal sequence of the V2 domain containing the tri-peptide sequence RDK at positions corresponding to 142 to 144 of MN-rgp120 [McKeating et al.; J. Virol. 67:4932-44 (1993); Moore et al.; J. Virol. 67:6136-6151 (1993)]. Like the C4 epitope, variation in this sequence is known to occur between different substrains derived from the same parental isolate. Since all seven breakthrough viruses differed from MN-rgp120 in that they possessed the RDK sequence, rather than the GDK sequence present in the vaccine antigen, neutralizing antibodies to the V2 domain of MN-rgp120 would not have been expected neutralize any of the viruses recovered from the vaccinees immunized with MN-rgp120.

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Although polymorphisms at neutralizing epitopes might account for the lack of protection in most of the infections, this does not appear to explain the 20 infection of vaccinee C17, who was infected by a virus that matched MN-rgp120 in the V3 and C4 domains. If a difference in sequence was responsible for the lack of protection in this case, the critical difference might relate to the unusual sequence in the V1 domain of gp120 from this breakthrough virus. Several studies have shown that the V1 domain possesses epitopes recognized by virus neutralizing monoclonal antibodies [McKeating et al.; J. Virol. 67:4932-44 (1993); Davis et al.; J. Gen. Virol. 74:2609-17 (1993); Kayman et al.; J. Virol. 68:400-410 (1994)].

Although far less is known about the V1 epitopes relative to other neutralizing sites, the V1 epitopes appear to be conformation-dependent, and antisera from HIV-1 infected individuals recognize epitopes in the V1 and V2 domains [McKeating et al.; J. Virol. 67:4932-44 (1993); Kayman et al.; J. Virol. 68:400-410 (1994)].

The V1 sequence of the virus from C17 is noteworthy because it is smaller and contains fewer N-linked glycosylation sites than that of MN-rgp120 or any of the other breakthrough viruses. By the same token, the envelope glycoproteins from C11 and C6 are noteworthy because they are significantly larger and contain more glycosylation sites than MN-rgp120 or the other breakthrough viruses.

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While differences in amino acid sequence can provide clues to differences in antigenic structure, the consequences of such polymorphism can only be proven through antibody binding studies. To correlate differences in sequence with differences in antigenic structure, gp120 from two clones each of all seven breakthrough viruses was expressed and the antigenicity of the clones with a panel of monoclonal antibodies was examined. As predicted from the sequence data, none of the breakthrough virus envelope glycoproteins reacted with neutralizing MAbs to the V2 domain of MN-rgp120. When MAbs to the C4 domain were examined, only the C17 envelope glycoprotein (that matched MN-rgp120 with respect to K429) showed significant, albeit lower, Surprisingly, the three breakthrough envelope glycoproteins that contained the subtype B PND consensus sequence, IGPGRAF (SEQ. ID. NO. !!), gave poor reactivity with all three PND directed MAbs, even though they possessed PND sequences closely related to the vaccine immunogen. Thus, all three of the vaccinee isolates appeared to possess changes outside of the recognition site that interfered with MAb binding.

It has been known for many years that resistance to neutralization in vitro can sometimes be attributed to mutations in remote sequences that alter the conformation of neutralizing epitopes and interfere with recognition by virus neutralizing antibodies [Nara et al.; J. Virol. 64:3779-91 (1990); Cordonnier

et al.; Nature 340:571-4 (1989)]. Together, these results indicate that the antigenic structure of the envelope glycoproteins recovered from the breakthrough viruses differed significantly from that of the vaccine antigen.

A novel result was the localization of residues in the C3 domain that appeared to affect the binding of the virus neutralizing human MAb, 15e. This MAb is known to recognize a discontinuous epitope, block CD4 binding, and neutralize a variety of laboratory and primary isolates of HIV-1 [Ho et al.; J. Virol. 65:489-93 (1991); Thali et al.; J. Virol. 66:5635-5641 (1992); Moore et al.; AIDS Res. Hum. Retroviruses 9:1179-1187 (1993)].

15 Comparative binding to envelope glycoproteins from the breakthrough viruses indicated that recognition by this antibody is critically dependent on residues in the C3 or C4 domains of gp120. The unique occurrence of a positively charged K at position 351 in the C3 domain provides a common explanation for the inability 20 of the C11.5, C11.7 and C6.1 strains of HIV-1 to bind to 15e. Alternatively, it is possible that different amino acid substitutions in different locations account for the failure of 15e to bind to rgp120s from the C6 and C11 clones. The only obvious positions where 25 substitutions of this type occur are in the C4 domain where T replaces M at 434 (C11) and T replaces I at 439.

The present studies demonstrate that the current formulation of MN-rgp120 is less than 100% effective against HIV-1 infection. Based on previous in vitro and in vivo studies with MN-rgp120, protection from natural HIV-1 infection in humans is expected to depend on a threshold concentration of virus-neutralizing antibodies, and antigenic similarity between the vaccine immunogen and the challenge virus.

In this regard, only one of the seven breakthrough infections (C17) was unexpected. This individual received a full course of immunizations yet became infected with a virus similar to MN-rgp120 at at least two important neutralizing epitopes (V3 and C4 domains). This infection might be related to the magnitude of the antibody response at the time of infection, or antigenic differences between the breakthrough virus and the vaccine strain, or circumstances of infection (e.g., ulcerative lesions, infection by donor with acute infection or high viremia), not monitored in this protocol. Alternatively this individual may represent a true vaccine failure, without clear explanation.

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On balance, the analysis of breakthrough infections described herein did not uncover any data that would discourage the continued development of MN-rgp120 as a vaccine to prevent HIV-1 infection. The results support speculation that enhancing vaccine immunogenicity (as by additional booster immunizations) may be required to maintain long term protective immunity, and that the addition of rgp120 from other antigenically different strains of virus in addition to MN-rgp120 are useful to expand the breadth of protection.

The availability of viruses and viral glycoproteins derived from breakthrough infections may provide an important means to streamline the process of identifying new antigens for inclusion into a multivalent vaccine. Recombinant viral glycoproteins prepared from breakthrough viruses, by definition, possess antigenic structures that are significantly different from MN-rgp120, and are be representative of viruses currently being transmitted. Thus, combining rgp120 from breakthrough viruses with MN-rgp120 is an effective way complement and significantly expand

antigenic complexity and increase breadth of cross
neutralizing activity.

SEQUENCE LISTING

```
(1) GENERAL INFORMATION:
         (i) APPLICANT: Berman, Phillip W.
          (ii) TITLE OF INVENTION: HIV ENVELOPE POLYPEPTIDES AND
                  VACCINE
        (iii) NUMBER OF SEQUENCES: 44
         (iv) CORRESPONDENCE ADDRESS:
             (A) ADDRESSEE: SKJERVEN, MORRILL, MACPHERSON, ET AL.
               (B) STREET: 25 Metro Drive, Suite 700
                (C) CITY: San Jose
                (D) STATE: California
               (E) COUNTRY: USA
                (F) ZIP: 95110
          (V) COMPUTER READABLE FORM:
               (A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
               (B) COMPUTER: IBM PC compatible
               (C) OPERATING SYSTEM: PC-DOS/MS-DOS
               (D) SOFTWARE: WinPatin (Genentech)
        (vi) CURRENT APPLICATION DATA:
                (A) APPLICATION NUMBER:
                (B) FILING DATE:
                (C) CLASSIFICATION:
        (VIII) ATTORNEY/AGENT INFORMATION:

(A) NAME: Terlizzi, Laura

(B) REGISTRATION NUMBER: 31,307
                (C) REFERENCE/DOCKET NUMBER: M-3897 US
          (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (408) 453-9200
             (B) TELEFAX: (408) 453-7979
      (2) INFORMATION FOR SEQ ID NO:1:
        (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 1503 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
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             (D) TOPOLOGY: Linear
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
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       Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
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       His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
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		40			ं विज्ञा ने		45		7,773			50		
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	GAT	TTT	AAC	ATG	TGG	AAA	AAT	GAC	ATG	GTA	CAA	CAG	ATC	192
10											Glu			102
		• • • • •		55		2,5		Р	60	• • •	O.Lu	, GIII	Hec	
					ang Pilit		•		. 00					
٠	CAT	CAC	דאת	מידמ	ATC	ACT	מידית	TCC	CAT	440	AGC	CTA	מממ	221
	His	Gla	Yaa	TIA	TIO	202	Lou	Tro	950	Cln	Ser	Lou	THE	231
15	65	014	Add.	110	116	70	.Deu	I.L.p	изъ	.G.111	75	Leu	гуз	
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	Dro.	Cva	V51	LUC	100	The	Dro.	LOU	Circ	110	Thr	. 114	NA1	270
	110	Cys	80		Leu	1111.	FEO	85	C y.s	116	1111	Leu	90	
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20	TGC	n.c.c	יי א א	TOO	220	CAC	ת ת ת	CAT	A CT		ACT.		N	200
	Cve	The	DUL	T 5 5	TWO	Clu	DO 1	GWI	The	T	Thr	AAI	AGT	309
	Cys	TILL	ASII	rrp	95	GIU	ASI	ASP	inr		Tur	ASN	ser	
					. 70					100				
25	3.00													- 0
25		AGT	ACT	ACA.	ACT	AAT	AAI	AGT	AGT	GCT	ACA	GCT	AAT	348
	Ser		Thr	Thr	Thr	Asn		Ser	ser	Ala	Thr		Asn	
		105		٠.	. 11.	i	110					115		•
						1.1						7		
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30	ser	ser				Thr	Asn	Ser		Trp	Gly	Glu	Ile	
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											AAT			426
2.5		Glu	G1.y	Glu	He			Cys	Ser	Phe	Asn	lle	Thr	
35	130				<i></i>	135	.* .				140			
				1	i.e. in					-	٠.			
. *											TAT			465
	Thr	Gly		Arg	Asp	Lys	Val	Lys	Lys	Glu	Tyr	Ala	Leu	
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40						a. 25 j								
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	Phe	Tyr	Ser	Leu		Val	Val	Pro	Ile		Asn	Asp	Asn	
					160					165	. 1.47			
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45											TCA			543
· .· .	Thr		Tyr.	Arg	Leu	Arg	Ser	Cys	Asn	Thr	Ser	Val	Ile	
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_1	ACA	CAA	CCC.	TGT	CCA	AAG	GTA	ACT	TTT	GAG	CCV	ATT	CCC	582
50	Thr	Gln	Ala	Cys	Pro	Lys	Val	Thr	Phe	Glu	Pro	lle	Pro	
				185					190		•			
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														621
		His	Tyr.	Cys	Thr	Pro	Ala	G1.y	Phe	Ala	Ile	Leu	Lys	
55	195				: "" .	200	:.				205			. :
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	TGT	AAA	GAT	AAA	AAG	TTC	AAT	GGA	ACA:	GGA :	CCA	TCC	AAA	660
	Cys	Lys	Asp	Lys	Lys	Phe	Asn	Gly	Thr	Cly	Pro	Cys	Lys	
			210					215		::: ⁷ .	11/2		220	
60	٠.		1	`	grafi.					1		· .•		
: :	AAT	GTT -	AGC	ACA	GTA:	CAA	TGT	ÁCA	CAT	GGA	ATT	AAG	CCA	699
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		GTA Val	Val	TCA Ser	ACT Thr	CAA Gln	CTG Leu	CTG Leu 240	TTA Leu	AAT Asn	GGC Gly	AGC Ser	CTA Leu 245	GCA Ala	738				* = .	
	5	GAA Glu	235 GAA Glu	GAG Glu	Val	ATA Ile	ATT Ile	AGA Arg	TCT Ser	Ala	AAT Asn	TTC Phe	TCA Ser	AAC Asn	777					***
	10	AAT Asn	GCT Ala	AAA Lvs	250 ATC Ile	ATA Ile	ATA Ile	GTA Val	CAG Gln	255 TTG Leu	AAG Lys	GAA Glu	CCT Pro	GTA Val	816					
	20	260	ልሞጥ	ААТ	тст	ACA	265 AGA	CCC Pro	AGC	AAC	AAT	ACA	ATA	AAA	855	ene Ene Toggen		1 		
	15	CCT	АТА	275 CAC	ATA	GGA	CCA	GGG	280 AGA	GCA	TTT	TAT	GCA	ACA	894					
	20	Gly	Ile	His	Ile	Cly 290	Pro	Gly	Arg	Ala	295	Tyr	Ala	Thr						
.*		Gly	300	Ile	Arg	G1 y	Asp	11e 305	Arg	Gln	Ala	His	310	Asn						· ()
	25	ATT	AGT Ser	GGA Gly	GCA Ala 315	AAA Lys	TGG Trp	AAT Asn	AAC	ACT Thr 320	TTA Leu	Lys	Lys	GTA Val	972	- 1.				
*.	30	GTT Val 325	ATA Ile	F\a Y\a	TTA Leu	AAA Lys	GAA Glu 330	CAA Gln	TTT Phe	CCA Pro	AAT	AAA Lys 335	ACA Thr	ATA Ile	1011			·		
	35	GTC Val	TTT Phe	AAC Asn 340	CAT His	TCC Ser	TCA Ser	GGA Gly	GGG Gly 345	GAC Asp	CCA Pro	GAA Glu	ATT Ile	GTA Val 350	1050					
		ATG Met	CAC His	AGT Ser	TTT Phe	AAT Asn 355	Cys	CAA Gln	GGG Gly	GAA Glu	TTT Phe 360	TTC Phe	TAC Tyr	TGT Cys	1089					÷
	40	AAT Asn	ACA Thr 365	ACG Thr	Lys	CTG Leu	TTT Phe	AAT Asn 370	Ser	Thr	TGG Trp	ASI	ASP	THE	1128					
	45	ACA Thr	GAG Glu	Ser	AAT Asn 380	Asn	Asn	GAT Asp	Ser	Thr	ATT Ile	ACA Thr	CTC Leu	CCA Pro	1167					
	50	Cys	AGA Arg	Ile	Lvs	CAA Gln	Ile	Ile	AAC Asn	ATG Met	TGG Trp	CAG Gln 400	GIU	GTA Val	1206					
	55	GGA Gly	AAA Lys	GCA Ala	ATG Met		GCC Ala	CCT Pro	CCC Pro 410	Ile	AGA Arg	GGA Gly	GIR	Tře	1245				1. 15. 15. 15. 15. 15. 15. 15. 15. 15. 1	*
	 !	AAA Lys	Cys	TCA Ser	TCA Ser	AAT Asn	ATT lle	ACA	Gly	Leu	CTG Leu 425	Len	ACA Thr	AGA Arg	1284					*: "
	60	GAT Asp	GGT	GGT	ATI Ile	AAC Asn	ACT Thr		GAT Asp	GCC	ACC	GAG	ACC Thr 440	TTC Phe	1323		erika uguzeak Bertantak Bertantak Pagapan ber Bertantak			

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	AGA	CCG	GGA	GGA	GGA	GAT	ATG	AGG	GAC	AAT	TGE	AGA	АСТ	136	9		
	Arg	Pro	Gly	Gly 445	Gly	Asp	Met	Arg	Asp 450	Asn	Trp	Arg	Ser				
5		Leu			TAT Tyr		Val								1		
10	GGA Gly	GTA Val	GCA Ala 470	Pro	ACC Thr	AAG Lys	GCA Ala	AAG Lys 475	AGA Arg	AGA Arg	GTG Val	GTG Val	CAG Gln 480	144	0		
1 5	AGA Arg	GAA Glu	AAA Lys	Arg	GCA Ala 485	Val	ACA Thr	CTA Leu	GGA Gly	GCT Ala 490	ATG Met	TTC Phe	CTT Leu	147	9		
20			Leu		GCA Ala			Pne	150	3		•			•		e i
20		i) Si	EQUE:	NCE ENGT	FOR S CHAR H: 50	ACTE! D1 ar	RISTI nino	cs:									
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40	Val	Glu	Gln	Met	50 His 65	1 1 1	Xaa	Ile	Ile	55 Ser 70	Leu	Trp	Asp	Ġļn	60 Ser 75		an ef an ef an ef ataken
	Leu	Lys	Pro	Cys	Val 80	Lys	Leu	Thr	Pro		Cys	Ile	Thr	Leu			
45	САа	Thr	Asn	Trp	Lys 95		Asn	Asp	Thr	Lys 100	Thr	Asn	Ser	Ser	Ser 105		
50	Thr	Thr	Thr	Asn	Asn 110	Ser	ser	Ala	Thr	Ala 115	Asn	Ser	Ser	Ser	Thr 120		
		: :	*		Ser 125	er e 1969 Manadê e e Staats e e				130					135		
55			٠.		140					145					150		
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		o 0.			170 Cys				*	175					180		· · ·
65		٠.			185	#**********************	0.			190	· - -		-		195		**

	His	Tyr	Сув	Thr	Pro	Ala	Gly	Phe	Ala	Ile 205	Leu	Lys	Cys	Lys	Asp 210
5	Lys	Lys	Phe	Asn	Gly 215	Thr	Gly	Pro	Cys	Lys 220	Asn	Val	Ser	Thr	Val 225
	Gln	Сув	Thr	His	Gly 230	lle	Lys	Pro	Val	Val 235	Ser	Thr	Gln	Leu	Leu 240
10	Leu	Asn	Gly	Ser	Leu 245	Ala	Glu	Glu	Glu	Val 250	Ile	Ile	Arg	Ser	Ala 255
15					260	Livin Liugij		Ile	٠.	265	• •	÷ .			270
***					275			Arg	• .	280					285
20				٠.	290			Arg	· .	295					300
	. : :	:			305		di.	Ala		310	٠.				312
25		٠.			320			Lys	÷ :	325			<i>y</i>		330
30					335			Val	· .	340	4	7	· :.		343
30					350	i		Ser		355					360
35		٠.			365	1		Leu		370	•	:'	•		3/5
					380					385		: 1.	1.5. 4.1.		Cys 390
40		-	_		395		K	Met		400					405
45					410			Gly		415		:		··	420
				• • •	425	THE STATE		Arg		430.	: .	٠	`i ;		4.3.5
50					440			Pro		445					450
	Asn	Trp	Arg		Glu 455		Tyr	Lys	Tyr	Lys 460	Val	Val	Lys	Ile	Glu 465
55	Pro	Leu	Gly	Val	Ala 470		Thr	Lys	Ala	Lys 475	Arg	Arg	Val	Val	Gln 480
60	Arg	Glu	Lys	Arg	Ala 485		Thr	Leu	Gly	Ala 490	Met	Phe	Leu	Gly	Phe 495
	Leu	Gly	Ala	Xaa		Phe 501									
. • • . • •	(2)	INFO	RMAT	ION	FOR	SEQ	ID N	0:5:					. 1		

(2) INFORMATION FOR SEQ ID NO:5: (i) SEQUENCE CHARACTERISTICS:

		(A) L	ENGT	H: 1	461	base	pai	rs			1	·	
	1		B) T											
			C) S					gle				.i ;***		
5	1		D) T					CPO	7.0	NO.E	11.1 Tyres 21.1			
	(**	113	EQUE	NCE	DESC	KIPI	TON	250		NO: 5	•			. L.
· · · · · · · ·	G	GTA	CCT	GTA	TGG	AAA	GAA	GCA	ACC	ACC	ACT	CITIA	Juliu	37
			Pro											- T.
		1				5			:500		10		:	
10	··· :.	1. ** :		.:				: [1.7		
	TGT	GCA	TCA	GAT	GCT	AAA	GCA	TAT	GAT	ACA	GAG	GTA	CAT	76
	Caa	Ala	Ser	Asp	Ala	Lys	Ala			Thr	Glu			
			15					20		•			- 25	
15	220	c mm	maia		202	0.0		mam		000				
10	Ven	Ua:1	TGG Trp	7:) a	Thr	LHIC	Ala	Cue	GIA Gun Y	Bro	The	GAC	CCC	112
	non	val	ı, p	n.a	30	1113	nra	Суз	vaı	35		nsp	PIO	
	AAC	CCA	CAA	GAA	GTA	GTA	TTG	GAA	AAT	GTA	ACA	GAA	AAT	154
20	Asn	Pro	Gln	Glu	Val	Val	Leu	Glu	Asn	Val	Thr	Glu	Asn	
		40	•	,			4.5				· .	50		
									: :::: , , .					. `
	TTT	AAC	ATG	TGG	AAA	TAA	AAC	ATG	GTA	GAA	CAG	ATG	CAT	193
25	Pne	Asn	Met		Lys	Asn	Asn	Met	·Val	Glu	Cln	Met	His	
25				55			4 :	4.1.	. 60			::		
	GÄĞ	CAT	ATA	איזיר	ACT	ጥጥል	TGG	САТ	CAA	АСТ	CTA	AAC	CCD	
			Ile											232
	65			. 7.		70	, 2-	. · · - . F .			75	-7-		
30					•				ur Pak. Til					••
	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	GTT	ACT	TTA	AAT	TGC	271
	Cys	Val	Lys		Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	Cys	
			80	٠.		-	:	85	. i.,		44 TY	100	90	
35			-											
3,5	Th.	AAT	TTG Leu	CAG	AAI	GCT	AAT	AAT	ACC	GAG	AAT	GCT	AAT	310
	THE	ASII	Leu	GIU	95	WIG	ASII	ASII	THE	100		ALA	ASN	- 1. f.,
					, , ,			. :	: 1	100	+			
	AAT	ACC	AAT	AAT	TAT	ACC	TTG	GGG	ATG	GAG	AGA	GGT	GAA	349
40			Asn											
		105					110					115		
				ii.						Marian	lib, it			
	ATA	AAA	AAC	TGC	TCT	TTC	TAA	ATC	ACC	ACA	ACC	TTA	AGA	388
45	тте	rys	Asn		ser	Phe	Asn			Thr	Ser	Leu	Arg	
40				120				1. 1. 1.	125		,:: ·:.···	11.		
	CAT	AAG	GTG	AAA	444	AAD	דביד	CCA	ттс	መ ጠመ	ጥልጥ	ΔΔΔ.	CTT	107
	Asp	Lvs	Val	Lvs	Lvs	Glu	Tvr	Ala	Leu	Phe	Tvir	Ivs	Leu	421
* : *	130		777	-4-		135	- 1 -		. T. T.		140		200	
50	** • :					٠.							٠	
	GAT	GTA	GTA	CAA	ATA	GAT	AAT	AGT	ACC	AAC	TAT	AGG	CTG	466
	Asp	Val	Val	Gln	Ile	Asp	Asn			Asn	Tyr	Arg		
and a silv		g 15	145			. :	r ky, r	150	L. I. : ji:	Halling.	T :		155.	
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			TGT											
	116	JEI	Cys		160		AGT	115		165	urq	Cy5	P.T.O	- ".
					100		· · · ; ; .	1, 1		100	., "i ii			
	AAG	GTA	TCC	TTT	GAG	CTA	ATT	CCC	ATA	CAT	TAT	TGT	GCC	544
60	Lys	Val	Ser	Phe	Glu	Leu	Ile	Pro	Ile	His	Tyr	Cys	Ala	i.
•		170		:			175				7	180	. :	
	- 1							e edil	34	1.11.11	na A			
	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAA	GAT	AAG	AAG	583
	Pro	Ala	Gly	Phe	Ala	Tle	Leu	Lys	Cys	Lys	Asp	Lys	Lys	

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i. ::::::::::::::::::::::::::::::::::::	TTC	AAT	GGA	ACA	GGA	CCA	TGT	AAA	AAT	CTC	AGC	ACA	GTA	622
	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	Asn	val	205	Thr	ABI	
	195					200	1753-7 11 1855			rurur Pili di	203	: :		
ė.	440	тст	404	ТАЭ	GGA	ATT	AGA	CCA	GTA	GTA	TCA	ACT	CAA	661
	Gln	Cvs	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	GIII	
	- 111		210					215					220	
	•	· · · ·	·		GGC		OMA	CCN	C D D	CAA	GAG	ATA	GTA	700
10	CTA	CTG	TTA	AAT	GGC	Sor	Teu	Ala	Glu	Glu	Glu	Ile	Val	
10	Leu	Leu	Leu	Vali	225	20.1				230				·
	·						•							7.20
	ATT	AGA	TCT	GAA	AAT	ATC	ACA	GAC	AAT	GCT	AAA	Thr	TIE	137
15	Ile		Ser	Glu	Asn	-11e	240	wab	ASII	VIG	Dy 3	245		
15	*	235						· ` .':.						
	ATA	GTG	CAG	CTA	AAT	GAA	TCT	ATA	GTG	ATT	AAT	TGT	ACA	778
	Ile	Val	Gln	Leu	Asn	Glu	Ser	Ile	val	Ile	Asn	Cys	Thr	
				250					255	::			;	
20	B-C B	000	እ:እ ጥ	א מימ	AAC	ACA	AGA	AAA	AGT	ATA	AAT	ATA	GGA	817
	ACA	Pro	Anı	Asn	Asn	Thr	Arg	Lys	Ser	Ile	Asn	Ile	Gly.	
	260					265			, e in e	•	270			
	٠							2.02	CCA	C A C	מידמ	מדמ	GGA	856
25	CCA	GGG	AGA	GCA	TTC Phe	TAT	Thr	Thr	Gliv	Asp	Ile	Ile	Gly	
	Pro	GIA	275	WIG	Pile	1 7 1		280					285	
1		. 8								art in Notation				005
	GAT	ATA	AGA	CAA	GCA	CAT	TGT	AAC	CTT	AGT	AAA	ACA	CAA	895
30	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	Leu	295	Lys	1111	GIII	
		··:			290				::'h. '.					
	TGG	GÀÀ	AAA	ACG	TTA	AGA	CAG	ATA	GCT	ATA	AAA	TTA	GAA	934
	Trp	Glu	Lys	Thr	Leu	Arg	Gln	Ile	Ala	Ile	Lys	Leu	Glu	
35		300			•		305		4 141,14			310		
	ÖNA	א א א	ጥጥጥ	ם מ	таа :	AAA	ACA	ATA	GCC	TTT	AAT	AAA	TCC	973
•	Glu	Lvs	Phe	Lys	Asn	Lys	Thr	Ile	-Ara	Phe	Asn	Lys	Ser	
				315			. " - 4		320	*1*				
40						C 2 2 2	አመጥ	ር ምል	ATC	CAC	AGT	ጥጥተ	AAT	1012
• •	TCA	GGA	GGG	GAC	Pro	GAM	TIE	Val	Met	His	Ser	Phe	Asn	
	325		GLY	NSP	PLU	330				dili je	335			
		·	٠				. 117						CHÍ C	1051
45	TGT	GGA	GGG	GAA	TTT	TTC	TAC	TGT	AAT	ACA	The	LVS	t:eu	1051
1	CAB	Cly	Gly 340	G1 u	Phe	Pne	ıyı	345	Nau				350	
								# T#15						
	TTT	TAA	AGT	ACC	TGG	PAAT	TTA	ACA	CAA	CCG	TTT	AGT	TAA	1090
50	Phe	Asn	Ser	Thr	Trp	Asn	Leu	Thr	GIn	360	Pne	Ser	Asn	
a di di di		1111			355	-		-111	100	300			:	
i)	ACC	GGG	ТАД	CG	ACT	GAA	GAG	TTA	AAT	TTA	ACA	CTC	CCA	1129
Et. 11	Thr	Glv	Asn	Arc	Thr	Glu	Glu	Leu	Asn	Ile	Thr	Leu	PLO	
55		365		•			3.70)*, † [*] . i.	* [11.11]		11.4 1185 - 1	375		
B						חייים) D TT N	מ מ	ጥጥር	TGG	CAG	GAA	GTA	1168
	TGC	AGA	ATA	AAA Tus	Glr	Tle	Ile	Asr	Leu	Trp	Gln	Glu	Val	·
	Cy S	9	- ++c	380			*	1	385					
60						* 				D.C. N	CON	CAA	שתה ע	1207
	GGC	AAA	GCP	ATO	TAT	GCC	CC	CCC	ATC ATTA	Arn	Glv	Glin	Ile	1207
	Gly	/ Lys	. Ale	Met	Tyr	395	, , , ,			9	400)		
	256		. :			77.			:::			• '		

1, 396,135 1, 396,135 1, 396,171 1, 31, 32, 32 1, 31, 33, 33											TTA Leu			124	6
5						Thr					ACT Thr			128	5
10											AAT Asn			132	4
15			Leu		Lys					Arg	ATT Ile			136	3
											AGA Arg 465			140	2
20											GCT Ala			144	1
25					Gly	GAT Asp 486		1461	·1						
30	(2)	L) SI	EQUE!	NCE C	CHAR 1: 48	SEQ ACTE B6 an	RIST mino	ICS:	ds						
:			D) TO							*		;			
35		L) SI	EQUE	VCE I	DESCI	RIPT	ION:								
35		L) SI	EQUE	VCE I	DESCI	RIPT	ION:					Phe	Cys	Ala	Ser 15
35 40	Val) SI Pro	Val	Trp	Lys 5	RIPT Glu	ION: Ala	Thr	Thr	Thr 10	Leu		+ 1	Ala	15
	Val 1	Pro Ala	EQUEI Val Lys	Trp Ala	Lys 5 Tyr 20	RIPT Glu Asp	ION: Ala Thr	Thr	Thr Val	Thr 10 His 25	Leu	Val	Trp		15 Thr 30
	Val 1 Asp	Pro Ala Ala	Val Lys Cys	Trp Ala Val	Lys 5 Tyr 20 Pro	RIPT Glu Asp Thr	ION: Ala Thr	Thr Glu Pro	Thr Val Asn	Thr 10 His 25 Pro 40	Leu Asn Cln	Val Glû	Trp	Ala	15 Thr 30 Leu 45
40	Val 1 Asp His	Pro Ala Ala Asn	Val Lys Cys Val	Trp Ala Val	Lys 5 Tyr 20 Pro 35 Glu 50	Glu Asp Thr	ION: Ala Thr Asp Phe	Thr Glu Pro Asn	Thr Val Asn Met	Thr 10 His 25 Pro 40 Trp 55	Leu Asn Cln	Val Glû Asn	Trp Val Asn	Ala Val	15 Thr 30 Leu 45 Val 60
40	Val 1 Asp His Glu	Pro Ala Ala Asn Gin	Val Lys Cys Val Met	Trp Ala Val Thr	Lys 5 Tyr 20 Pro 35 Glu 50 Glu 65	Glu Asp Thr Asn	ION: Ala Thr Asp Phe	Thr Glu Pro Asn Ile	Thr Val Asn Met Ser	Thr 10 His 25 Pro 40 Trp 55 Leu 70	Leu Asn Cln Lys	Val Glû Asn Asp	Trp Val Asn	Ala Val Met Ser	15 Thr 30 Leu 45 Val 60
440 445	Val 1 Asp His Glu Glu	Pro Ala Ala Asn Gin	Val Lys Cys Val Met	Trp Ala Val Thr His	Lys 5 Tyr 20 Pro 35 Glu 50 Glu 65 Lys	Glu Asp Thr Asn Asp	ION: Ala Thr Asp Phe Ile	Thr Glu Pro Asn Ile Pro	Thr Val Asn Met Ser Leu	Thr 10 His 25 Pro 40 Trp 55 Leu 70 Cys 85	Leu Asn Cln Lys Trp	Val Glû Asn Asp	Trp Val Asn Gln	Ala Val Met Ser	15 Thr 30 Leu 45 Val 60 Leu 75 Cys
4.0 4.5	Val 1 Asp His Glu Clu Lys	Pro Ala Ala Asn Gin Pro	Val Lys Cys Val Met Cys	Trp Ala Val Thr His	Lys 5 Tyr 20 Pro 35 Glu 50 Glu 65 Lys 80 Asn 95	Glu Asp Thr Asn Asp Leu	ION: Ala Thr Asp Phe Ile Thr	Thr Glu Pro Asn Ile Pro	Thr Val Asn Met Ser Leu	Thr 10 His 25 Pro 40 Trp 55 Leu 70 Cys 85 Glu 100	Leu Asn Cln Lys Trp Val	Val Glû Asn Thr	Trp Val Asn Cln Leu	Ala Val Met Ser	15 Thr 30 Leu 45 Val 60 Leu 75 Cys 90 Thr 105
4.0 4.5	Val 1 Asp His Glu Clu Lys Thr	Pro Ala Ala Asn Gin Pro Asn	Val Lys Cys Val Met Cys Leu	Trp Ala Val Thr His Val Glu	Lys 5 Tyr 20 Pro 35 Glu 50 Glu 65 Lys 80 Asn 95 Leu 110	Glu Asp Thr Asn Asp Leu Ala Gly	ION: Ala Thr Asp Phe Ile Thr Asn Met	Thr Glu Pro Asn Ile Pro Asn Glu	Thr Val Asn Met Ser Leu Thr	Thr 10 His 25 Pro 40 Trp 55 Leu 70 Cys 85 Glu 100 Gly 115	Leu Asn Cln Lys Val	Val Glû Asn Thr	Trp Val Asn Cln Leu	Ala Val Met Ser Asn	15 Thr 30 Leu 45 Val 60 Leu 75 Cys 90 Thr 105 Cys 120
4.0 4.5 5.0	Val 1 Asp His Glu Clu Lys Thr	Pro Ala Ala Asn Gin Pro Asn Asn	Val Lys Cys Val Met Cys Leu Tyr	Trp Ala Val Thr His Val Glu Thr	Lys 5 Tyr 20 Pro 35 Glu 50 Glu 65 Lys 80 Asn 95 Leu 110 Thr 125	Glu Asp Thr Asn Leu Ala Gly	ION: Ala Thr Asp Phe Ile Thr Asn Met	Thr Glu Pro Asn Ile Pro Asn Glu Leu	Thr Val Asn Met Ser Leu Thr Arg	Thr 10 His 25 Pro 40 Trp 55 Leu 70 Cys 85 Glu 100 Gly 115 Asp 130	Leu Asn Cln Lys Val Asn Clu	Val Asn Asp Thr Ala Val	Trp Val Asn Lys	Ala Val Met Ser Asn	15 Thr 30 Leu 45 Val 60 Leu 75 Cys 90 Thr 105 Cys 120 Glu 135

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X + 8.	15	Ser	Leu	Ala	Glu	Glu 230	Glu	Ile	Val.	Ile	Arg 235	Ser	Glu	Asn	Ile	Thr 240
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	25	Ile	Gly	Pro	Gly	Arg 275	Ala	Phe	Tyr	Thr	Thr 280	Gly	Asp	Ile	Ile	Gly 285
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	50	Lys	Ala	Met	Tyr	Ala 395	Pro	Pro	Ile	Arg	Gly 400	Gln	Ile	Arg	Cys	Ser 405
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	40	ATA Ile	His	ATA Ile 275	Gly	CCA Pro	Glv	Ser	GCA Ala 280	Phe	Pne	GCA Ala	Inr	GIA	855		
	45	GAA Glu	ATA Ile	ATA Ile	GGA Gly	GAT Asp 290	Ile	AGA Arg	CAA Gln	ATA	CAC His 295	Cys	AAC Asn	CTT Leu	894		
	50	AGT Ser	AGA Arg 300	Thr	CAA Gln	TGG Trp	AAT Asn	AAC Asn 305	Thr	TTA Leu	GGA Gly	AAG Lys	ATA Ile 310	var	933		· · · · · · · · · · · · · · · · · · ·
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15	Glu	Val	Phe	Arg	Pro 440		Gly	Gly	Asp	Met 445	Arg	Asp	Asn	Trp	Arg 450
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20	Val	Ala	Pro	Thr	Lys 470	Ala	Lys	Arg	Arg	Val 475		Gln	Arg	Glu	Lys 480
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50 55	GAT ASP GAA Glu ATG Met	CCC Pro 40 AAT Asn	AAC Asn TTT Phe	CCA Pro AAC Asn	Trp 30 CAA Gln ATG Met	Ala GAA Glu TGC Trp ATC	Thr GTA Val 45 AAA Lys	GTA Val AAT ASD	TTG Leu AAC Asn 60	Cys 35 GGA Gly ATG Met	AAT ASN GTA Val	Pro GTG Val 50 GAA Glu	Thr ACA Thr CAA Gln	153 192	
	GAA GAA Glu ATG Met 65	CCC Pro 40 AAT Asn CAT His	AAC Asn TTT Phe GAA Glu	CCA Pro AAC Asn 55	Trp 30 CAA Gln ATC Met ATA Ile	Ala GAA Glu TGG Trp ATC Ile 70	Thr GTA Val 45 AAA Lys AGT Ser	GTA Väl AAT Asn TTA Leu	Ala TTG Leu AAC Asn 60 TGG Trp	Cys 35 GGA Gly ATG Met GAT Asp	AAT ASN GTA Val CAA Gln 75	Pro GTG Val 50 GAA Glu AGT Ser	Thr ACA Thr CAA Gln CTA Leu	153 192 231	

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	5	GAA Glu 260	Ile	AAT Asn	TGT Cys	ATA Ile	AGA Arg 265	CCC Pro	AAC Asn	AAT Asn	AAT Asn	ACA Thr 270	Arg	AAA Lys	818				
	10	GGT	ATA Ile	CAT His 275	Ile	GGA Gly	CCA Pro	GGG Gly	AGA Arg 280	GCA Ala	TGG	TAT Tyr	GCA Ala	ACA Thr 285				* 	
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	60	Glu	AGC Ser 430	Ser	ACT Thr	ACT Thr	Glu	ACC Thr 435	Phe	Arg	Pro	Gly	GGA Gly 440	Gly	1325				
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5	Leu Leu Leu	Asn G1 23	-00	Leu	Ala	Glu	Glu 235	Glu	Val	Val	Ile	Arg 240
	Ser Asp Asn	Phe Il		Asn	Thr		Thr 250	Ile	Ile	Val	Gln	Leu 255
10	Lys Glu Ser	Val Gl		Asn	Cys	Ile	Arg 265	Pro	Asn	Asn	Asn	Thr 270
	Arg Lys Gly	Ile Hi		Gly	Pro	Gly	Arg 280	Ala	Trp	Tyr	Ala	Thr 285
15	Gly Glu Ile	Val Gl		I,le	Arg	Lys	Ala 295	Tyr	Cys	Asņ	Ile	Ser 300
20	Arg Thr Lys	Trp Ass		Thr	Leu	Ile	Gln 310	Ile	Ala	Asn	Lys	Leu 315
	Lys Clu Lys	Tyr Ası		Thr	lle	Ser	Phe 325	Ysv	Arg	Ser	Ser	Gly 330
25	Gly Asp Pro	Glu Ile 33		Thr	His	Ser	Phe 340	Asn	Cys	Gly	Gly	Glu 345
30	Phe Phe Tyr	Cys Asj		Thr	Gln	Leu	Phe 355	Asn	Ser	Thr	Trp	Asn 360
	Leu Asn Gly	Thr Tri		Phe	Thr	Ala	Gly 370	Ser	Asn	Glu	Thr	Glu 375
35	Gly Asn Ile	Thr Le		Cys	Arg	Ile	Lys 385	Gln	Ile	Ile	Asn	Arg 390
*	Trp Gln Glu	Val G1:		Ala	Met	Туг	Ala 400	Pro	Pro	Ile	Ser	Gly 405
40	Gln Ile Lys	Cys Ser 410		Asn	Ile	Thr	Gly 415	Met	Ile	Leu	Thr	Arg 420
45	Asp Gly Gly	Asn Glu 42		Asn	Asn	Glu	Ser 430	Ser	Thr	Thr	G1u	Thr 435
	Phe Arg Pro	Gly Gly		Asp	Met	Arg	Asn 445	Asn	Trp	Arg	Ser	Glu 450
50	Leu Tyr Lys	Tyr Lys		Val	Lys	Ile	Glu 460	Pro	Leu	Gly	Val	Ala 465
	Pro Thr Lys	Ala Lys		Arg	Val	Val	Gln 475	Arg	Glu	Lys	Arg	Ala 480
55	Val Gly Ala	Leu Gly 48		Met	Phe	Leu	Gly 490	Phe	Leu	Gly	Ala	Xaa 495
60	Ser Phe Xaa	Thr Asi		Arg	Gly	Ser 504		`. <u>.</u>				*
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(D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

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	2.0	CCC Pro	Asn	Pro	CAA Gln	GAA Glu	ATA Ile	GAA Glu 45	TTG Leu	GTA Val	AAT Asn	CTG Val	ACA Thr	GAA Glu	15
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	35	Cys	AGT Ser	GAT Asp	GTG Val	AAC Asn 95	AÁT Asn	TCC Ser	ACA Thr	AAT Asn	CCT Pro 100	non	GAT Asp	ACT Thr	30
	40	AAT Asn	ACT Thr 105	Asn	TCC Ser	ACT Thr	AAT Asn	ACT Thr 110	Thr	TCC Ser	TCT Ser	7.111	CCT Pro 115		34
*		GCC Ala	3 CM	n CT	Ser	AGC Ser	GAG Glu	GAA Glu	AAG Lys	ATG Met 125	GAG Glu	AAG Lys	GGA Gly	GAA Glu	38
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	Leu	Lys	Pro	Cys	Val 80	Lys	Leu	Thr	Pro	Leu 85	Сув	Val	Thr	Leu	Asn 90
5	Cys	Ser	Asp	Val	Asn 95	Asn	Ser	Thr	Asn	Pro 100	Asn	qaA	Thr	Asn	Thr 105
	Asn	Ser	Thr	Asn	Thr 110	Thr	Ser	Ser	Thr	Pro 115	Thr	Ala	Thr	Thr	Ser 120
10	Ser	G1u	Glu	Lys	Met 125	Glu	Lys	Gly	Glu	11e 130	Lys	Asn	CAa	Ser	Phe 135
16	Asn	Ile	Thr	Thr	His 140	Met	Lys	Asp	Lys	Val 145	Gln	Lys	Glu	Tyr	Ala 150
15	Leu	Phe	Tyr	Lys	Leu 155	Asp	Ile	Val	Pro	11e 160	Asp	Asp	Asn	Asņ	Thr 165
20	Ser	Tyr	Arg	Leu	Ile 170	Ser	Cys	Asn	Thr	Ser 175	Val	Ile	Thr	Gln	Ala 180
	Сув	Pro	Met	Val	Thr 185	Phe	Glu	Pro	Ile	Pro 190	Ile	His	Tyr	Cys	Ala 195
25	Pro	Ala	Gly	Phe	Ala 200	Ile	Leu	Lys	Cys	Lys 205	Asp	Lys	Lys	Phe	Asn 210
20	Glÿ	Thr	Gly	Pro	Cys 215	Ser	Lys	Val	Ser	Thr 220	Val	Gln	Сув	Thr	His 225
30	Gly	Ile	Arg	Pro	Val 230	Val	Ser	Thr	Gln	Leu 235	Leu	Leu	Asn	Gly	Ser 240
3.5	Leu	Ala	Glu	Glu	Glu 245	Val	Val	Ile	Arg	Ser 250	Val	Asn	Phe	Thr	Asp 255
	Asn	Ala	Lys	Ile	Ile 260	Ile	Val	Gln	Leu	Lys 265	Glu	Pro	Va 1	Ala	11e 270
40	Asn	Cys	Thr	Arg	Pro 275	Asn	Asn	Asn	Thr	Arg 280	Lys	Gly	Ile	His	Leu 285
	Gly	Pro	Gly	Ser	Thr 290	Phe	Tyr	Thr	Thr	Gly 295	Glu	Ile	Ile	G1ÿ	Asp 300
45	Ile	Arg	Lys	Ala	Tyr 305	Cys	Lys	Ile	Ser	Lys 310	Glu	Lys	Trp	Asn	Asn 315
50	Thr	Leu	Arg	Gln	Val 320	Val	Lys	Lys	Leu	Arg 325	Glu	Gln	Phe	Gly	Asn 330
	Lys	Thr	Ile		Phe 335		Arg	Ser	Ser	Gly 340		Asp	Pro	Glu	11e 345
55	Val	Met	His	Ser	Phe 350	Asn	Cys	Gly	Gly	Glu 355	Phe	Phe	Tyr	Сув	Asn 360
	Thr	Thr	Gln	Leu	Phe 365	Asn	Ser	Thr	Trp	Asn 370		Thr	Glu	Gly	Thr 375
60	Asn	Ser	Thr	Glu	Gly 380		Ser	Thr		Thr 385	Leu	Pro	Сув	Arg	Ile 390
65	Lys	Gln	Ile	Ile	Asn 395		Trp	Gl'n	Glu		Gly		Ala	Thr	Tyr 405
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Ala Pro Pro Ile Arg Gly Arg Il Arg Cys Ile Ser Asn Ile Thr
410 415 420

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	Ala	Pro	Pro	Ile	Arg	Gly	Arg	11	Arg	Cys 415	Ile	Ser	Asn	Ile	Th: 420
	1,				410								mik e	A C D	Acr
5	Gly	Leu	Leu	Leu	Thr 425	Arg	Asp	GIA	GIA	430	ASN	val	THE	ASII	435
	Thr	Xaa	Xaa	Phe	Arg	Pro	Gly	Gly	Gly	Asp	Met	Arg	Asp	Asn	Tr
			: '	1.5	440				·	443					
10	Arg	Ser	Glu	Leu	Tyr 455	Lys	Tyr	Lys	Val	Val 460	Lys	Val	Glu	Pro	Le:
				:					N = 0	λ ~ α	Val	Val	ніс	Ara	Ası
	Gly	Ile	Ala	Pro	470	r.y.s.	Ala	Lys	urg	475		•••			480
15	Lvs	Arq	Ala	Ala	Leu:	Gly	Ala	Leu	Phe	Leu	Gly	Phe	Leu	Gly	Al
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	Xaa	Lys	Leu	Leu 499				4	r						
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	(2)	i 1 S	EQUE	NCE (	CHARA	ACTE	ID NO RIST	ICS:		: .					•
		Ċ	A) L	ENGT	1: 14	175	base Acid	pain	cs.	•	<i>:</i> -				
25			CY S'	TRANI	DEDNI	ESS:	Sing	jle.			: :				•
	. (v	) () 33 S	D) TO	OPOLO	OGY: DESCI	Lin RIPT	ear ION:	SEQ	İD	NO: 2	1:		٠.	٠	
							GAA	11.				СТА	TTT	3:7	,
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	* • .	1			*	5					10				
	TGT	GCA	TCA	GAT	GCT	AAA	GCA	TAT	GAT	AGA	GAA	GTA Val	CAT	76	
35	Cys	Ala	Ser 15	Asp	Ala	Lys	Ala	20	ASP	ALG	GIU	V41	25		
	2.00		TCC	CCA	A C A	САТ	GCC	TGT	GTA	CCC	ACA	GAC	CCC	115	: ' . '.
	AAI	. Val	Trp	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro		•
40			. '		30			of Halik Halikota				٠.		٠.	. · :
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	Phe	Asr	Met	Trp	Lys	Asr	Asn	Met	Val 60	Gru	Gln	Met	His	• • • • •	: ::
tadyd Tadyd		":		55									CCN	222	,
50	GAC	GAT	ATA	ATC	AAT	TT?	TGG Trp	GAT Asp	Gln	Ser	Leu	Lys	Pro		
	6					7.0	)				75				
	TG	GT/	AAC	TTA	ACT	CCI	CTC	TGT	GTI	ACT	TTA	AAG	TGC	271	
55	Cy	va.	Lys 80	Leu	Thr	Pro	) Leu	Cys 85	v a 1	ı'nı	reu	n Dys	90		
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65				.1.1				-:	.:::				1.		1.0

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				120			e di in in		125			7.7		
5	מממ	CTC	CNC	222	CAA	TAT	400	CTT	ጥጥር	: ጥልጥ	202	CTT	CAT	<b>7.27</b>
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10								Asp						400
	्राच्या इ.स.च्या		145					150					155	
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25.								TGT Cys						022
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	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	G]·u	Glu	Val	700
35				· ".	225					230			- 11	
	CTA	ATC	ACA	: :ጥርጥ	ede	AAT	TTC	ACA	GAC	AAT	GCT.	AAA	ACC	739
								Thr						
4.0		235	3 3				240					245		
40	ATA	ATA	GTA	САТ	CTA	ААТ	GAA	ACT	GTA	AAA	TTA	AAT	TGT	778
. :								Thr	Val					36.5
				250			in in a second		255	, ,	1. 1.			
45	ACA	AGA	CTT	GGC	AAC	AAT	ACA	AGA	AAA	AGT	λΤΑ	АЛТ	ATA	817
								Arg						15
	260	1	ight the			265		h . **	:		270			
	CGA	CCA	GGG	AGA	GTA	CTC	TAT	GCA	ACA	GGA	GAA	ATA	ATA	856
50								Ala					Ile	
			275	11 11 2		• • . • •		280		. :	-		285	
	GGA	GAC	ATA	AGA	CAA	GCA	CAT	TGT	AAC	ATT	AGT	AGA	CCA	895
	Gly	Asp	Ile	Arg		Ala	His	Cys	Asn		Ser	Arg	Ala	ar in a r Table in the
55		`		'n	290					295	·			
1.11.51	CAA	TGG	AAT	AAG	ACT	TTA	GAA	AAG	GTA	GTT	GAC	AAA	TTA	934
		Trp	Asn				Glu	Lys				Lys		
60		300				. * .	305					3:10		o.
	AGA	AAA	CAA	TTT.	GGG	GAT	AAT	ACA	A'CA'	ATA	GCT	TTT	AAT	973
			Gln	Phe				Thr	Thr					
			n. t. Hijan	315					320	8		٠.	: "	- 11.

	CCA	TCC	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GTA	ATG	CAC	ACT	1012	
	Arg 325	Ser	Ser	Gly	GIA	330	Pro	Gin	116	V.4.1	335				
5	TTT Phe	Asn	TGT Cys 340	GGA Gly	GGG Gly	GAA Glu	Phe.	TTC Phe 345	TAC Tyr	Cys	AAT Asn	ACA Thr	ACA Thr 350	1051	
10	CAA Gln	CTG Leu	TTT Phe	AAT Asn	AGT Ser 355	ACT. Thr	TGG Trp	TAA Asn	TAA nea	ACT Thr 360	TGG Trp	AAG Lys	GAT Asp	1090	
15	Pro	AAC Asn 365	AGG Arg	AGT Ser	GAC Asp	TAA Asn	ATC Ile 370	Thr	CTC Leu	CCA Pro	Cys	AGA Arg 375	ATA	1129	:
	AAA Lys	CAA Gln	ATT Ile	ATA Ile 380	Asn	ATG Met	TGG Trp	CAG Gln	GAA Glu 385	GTA Val	GGA Gly	AAA Lys	GCA Ala	1168	· .
20	ATG Met 390	Tyr	GCC Ala	CCT	CCC Pro	ATC Ile 395	AGA Arg	GGG Gly	GAA Glu	Tie.	AGA Arg 400	Cys	TCA Ser	1207	
25	mos	N D TT	ATC Ile 405	Thr	GGG Gly	CTG Leu	CTÀ Leu	CTA Leu 410	ACA Thr	AGA Arg	GAT Asp	GGT Gly	GGT Gly 415	1246	
30	AAT Asn	GAC Asp	C N T		AAT Asn 420	Asp	ACG Thr	ACC Thr	ACA Thr	AAC Asn 425	ALG	ACC Thr	GAG Glu	1285	:
95	ATC Ile	TTC Phe 430	Arg	CCT Pro	CCA	GGA	GGA Gly 435	Asp	ATG Met	AGG Arg	GAC Asp	AAT Asn 440	12 [	1324	i.
35	AGA Arg	<b>.</b>	<b>63.</b> N	TTA Leu 445	Tyr	AGA Arg	TAT Tyr	AAA Lys	GTA Val 450	Agr	AAA Lys	ATT Ile	GAA Glu	1363	
40	Pro	Leu	GGA Gly	מית	GCA	CCC Pro	Thr	AGG Arg	GCA Ala	AAG Lys	AGA Arg 465	nr 9	GTG Val	1402	
45	455 GTG Val		AGA Arg	Gli	AAA Lys	D.C.A.	CCCA	GTA Val 475	Gry	CTA Leu	GGA Gly	GCT Ala	TTG Leu 480	1441	
50	TTC		GGC	3 T T	CTTA	NGGAG	CAT	PAAAG	CTT	CTAG	A 14	75			
55	(2)	(1)	ORMA SEQUI	TION ENCE LENG'	TH: 4	SEQ RACTE 191 a	mino	aci							
		ci) S	(D) SEQUI	TOPO ENCE	DESC	: Lir CRIP	rear rion:	: SEC		11		i Phe	e Cve	Ala	Ser
60		1	1			5				110		4.		Ala Ala	
- 65	Asi	p Al	a Ly	s Al	a Ty:	) O	) ME	, 011	. •	25					3.0

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	His	Ala	Cys	Val	Pro 35	Thr	Asp	Pro	Asn	Pro 40	Gln	Glu	Ile	Val	Leu 45
. 5	Gly	Asn	Val	Thr	Glu 50	Asn	Phe	Asn	Met	Trp 55	Lys	Asn	Asn	Met	Val 60
	Glu	Gln	Met	His	Glu 65	Asp	Ile	Ile	Asn	Leu 70	Trp	Asp	Gln	Ser	Leu 75
10	Lys	Pro	Cys	Val	Lys 80	Lėu	Thr	Pro	Leu	Cys 85	Val	Thr	Leu	Lys	Cys 90
	Lys	Asp	Leu	Glu	Arg 95	Asn	Thr	Thr	Tyr	Asn 100	Ser	Thr	Ile	Thr	Asn 105
15	Asn	Ser	Ser	Leu	Glu 110	Gly	Leu	Arg	Glu	Gln 115	Met	Thr	Asn	Cys	Ser 120
20	Phe	Asn	Ile	Thr	Thr 125	Ser	Ile	Arg	Asp	Lys 130	Val	Gln	Lys	Glu	Tyr 135
	Ala	Leu	Leu	Tyr	Lys 140	Leu	Asp	Val	Val	Pro 145	Ile	Glu	Glu	Asp	Asp 150
25	Asn	Thr	Ser	Tyr	Arg 155	Leu	Ile	Ser	Cys	Asn 160	Thr	Ser	Val.	Ile	Thr 165
30	Gln	Ala	Cys	Pro	Lys 170	Thr	Ser	Phe	Glu	Pro 175	Ile	Pro	Ile	His	Tyr 180
• • • • • • • • • • • • • • • • • • •	Cys	Ala	Pro	Ala	Gly 185	Phe	Ala	lle	Leu	Lys 190	Cys	Asn	Asp	Lys	Lys 195
35	Phe	Asn	Gly	Thr	Gly 200	Pro	Cys	Lys	Asn	Val 205	Ser	Thr	Val	Gln	Cys 210
in is vei Pitenius Turavitai	Thr	His	Gly	Ile	Arg 215	Pro	Val	Val	Ser	Thr 220	Gln	Leu	Leu	Leu	Asn 225
40	Gly	Ser	Leu	Ala	Glu 230	Glu	Glu	Val	Val	Ile 235	Arg	Ser	Ala	Asn	Phe 240
45	Thr	Asp	Asn	Ala	Lys 245	Thr	lle	Ile	Val	His 250	Leu	Asn	Glu	Thr	Val 255
	Lys	Ile	Asn	Cys	Thr 260	Arg	Leu	Gly	Asn	Asn 265	Thr	Arg	Lys	Ser	Ile 270
50	Asn	Ile	Gly	Pro	Gly 275	Arg	Val	Leu	Tyr	Ala 280	Thr	Gly	Gl u	Ile	Ile 285
	Gly	Asp	Ile	Arg	Gln 290	Ala	His	Cys	Asn	Ile 295	Ser	Arg	Ala		Trp 300
55	Asn	Lys	Thr	Leu	Glu 305	Lys	Val	Val	Asp	Lys 310	Leu	Arg	Lys	Gln	Phe 315
60	Gly	Asp	Asn	Thr	Thr 320	Ile	Ala	Phe		Arg 325	Ser	Ser	Gly	Gly	Asp 330
	Pro	Glu	Ile	Val	Met 335	His	Thr	Phe		Cys 340	Gly	Glÿ	Glu	Phe	Phe 345
65	Tyr	Cys	Yau	Thr	Thr 350	G1n	Leu	Phe	Asn	Ser 355	Thr	Trp	Asn	Asn	Thr 360

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ga (1945) (1956) a seguina (1956) Caloning Baran (1956) a seguina (1956) Garan Gran (1956) a seguina (1956)						- 11								***				
	Trp	Lys	Asp I	Pro A	sn i	Arg	Ser	Asp	Asn	11e	Thr	Leu	Pro	Cys	Arg	. ii.i .:		
				3 Ile I	65			TYN	C) n	370	Val	Glv	Lvs	Ala				
5					во					363				."				
	Tyr	Ala	Pro I	Pro I	le . 95	Arg	Gly	Glu	Ile	Arg 400	Cys	Ser	Ser	Asn	11e 405			
	Thr	Glv	Leu I	Leu L	eu '	Thr	Arg	Asp	Gly	Gly	Asn	Asp	Asp	Gly	Asn			
				4	10					413	*							
	Asp	Thr	Thr '	Thr A	sn 25	Arg	Thr	Glu	116	430	Arg	Pro	-СТУ	GIA	435			
<b>15</b>	Asp	Met	Arg A	Asp A	sn 40	Trp	Arg	Ser	Glu	Leu 445	Tyr	Arg	Tyr	Lys	Val 450			
	Vai	Lve	Tlei	Glu P		Leu	Glv	Ile	Ala	Pro	Thr	Arg	Ala	Lys	Arg	·		
20				. 4	55				ė .	460				. •	403	 		
	Arg	Val	Val:	Gln A	rg 170	Glu	Lys	Arg	Ala	Val 475	Gly	Leu	Gly	Ala	480	·	· .	
25	Phe	Leu	Gly	Phe I		Gly	Ala	Leu	Phe	Leu	Gly			·.				
	(2)	NEOE	M N TO T	ON FO	185 np. s	ro 1	ות אונ	) : 23	a ie				· '	•:				
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3.0	•	( E	) TY () ST	PE: N	Nuc l EDNE	eic SS:	Sin	<b>d</b>				e deser Telegraphic	170					
n in the same of t	(· <b>x</b> :	ίτ	) TO	POLOC	GY:	Line	ear -		ID I	NO: 2	3:							٠.
3.5 ·	G	GTA	CCT	GTG 1	rgg	AAA	GAA	GCA	AAC	ACA	ACT	CTA	TTT	37		ing said	¥.,	
	• • • • • • • • • • • • • • • • • • • •	Val	Pro	Val 1	rrp	Lys 5	Glu	Ala	ASII	1111	10	Ded	1.1.0					
40	TGT	GCA	TCA	GAT G	GCT	AAA,	GCA Ala	TAT	GAT	AGA	GAA Glu	GTA Val	CAT His	76				
			15		· :	•		20					2.3	· · · ·				
4.5	AAT Asn	GTT Val	TGG Trp	GCA A	ACA Thr	CAT His	GCC Ala	TGT Cys	GTA Val	PFO	inr	GAC Asp	Pro	115				
			*:* .		30		·				Potriliais Talan				·	:: :		•
교육하다 아름이 발표하는 것 이 기계를 받는 기업 보다 기업 및 1000년	AAC Asn	Pro	Gln-	GAA Glu	ATA Ile	GTA Val	Leu	Gly	YSU	Val	Thr	Glu 50	Wall			· · ·		
50	ሙሙው	40	, .	TGG	 AAA	ААТ	. 45	ATC	GTA	GAA	CAA	# 1777 		193			1. 7 .	
	Phe	Asn	Met	Trp 55	Lys	Asn	Asn	Met	Val 60	GIU	Gln	Met	His	. · . Salaa				
55	GAG	GAT	מדמ	ATC	AAT	TTA	TGG	GAT	CAA	AGC	тта	AAG	CCA	232				
	Glu 65	Asp	Ile	Ile	Asn	Leu 70	Trp	Asp	Gln	Ser	Leu 75	Lys	Pro					
60			·		1-22					2.00	erm n	220	TCC	271				
60	TGT	GTA	AAG	Leu	ACT	CCA	CTC	TGT	GTT Val	Thr	Leu	Lvs	Cvs					

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V. Jedici	DAG	CAT	СТС	GÁG	ACC	TAA	ACT	ACC	ТАТ	AAT	ACC	ACT	TTA	310
					Arg									
					95	••••				100	:			
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.5	ACC	TAA	AAT	AGT	AGT	TTG	GAG	GGA	CTA	AGA	GAA	CAA	ATG	349
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		105	1 1	. ·			110	٠.				115		
			17.				^ · · · · · · · · ·	100	• .:		: .			
														388
10	Thr	Asn	Cys		Phe	Asn	Ile	Thr		Ser	Ile	Arg	Asp	
				120			•		125					10.10
														for the
					GAA									
			Gln	Lys	Glu		.Ala	Leu	Leu	Tyr	•	Leu	Asp	:: ··
15	130	W.				135					140			. 1 - 1
	OFFIX	OM N	.000	2003	~ ~ ~	CDD	CAM	C 1 C	N: N (T)	. cm	200		5.00	
					GAA									466
	AGT	Val	145	1.16	Glu	GIU	Asp	150	ASII	1.117	261	Lyr	155	
20		٠.	143				. 55	.130				٠	133	
20	TTG	474	ACT	TCT	AAC	DOG.	TCA	GTC	ΑΤΤ	474	CAG	CCT	тст.	505
· ···i.					Asn									303
		110	Jer	Cys	160		561		-116	165		n La	Cys	
* 6 * 4.	1	1			100	٠				107		;		
25	CCA	AAG	ACA	TCC	TTT	GAG	CCA	ATT	CCC	ATA	CAT	TAT	тст	544
-FF. 1					Phe									. F. 1 100
	1,1: ::	170					175	· .				180		4. F.
	Para di Para d					, .	. : .			•	* :		11.1	1.0
	GCC	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAT	GAT	AAG	583
3:0	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	Asp	Lys:	
				185			- 2		190		1.1	. : -		
	: Siz		- 1:		•								- 11	
• * * . *					ACA									622
		Phe	(Asn	Cly	Thr		Pro	Cys	Lys	Asn		Ser	Thr	
35	195					200					2.05	9.49		
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1.112.4.42					CAT									991
ti grafisk	vaı	GIn	210		His	GIY	TIE	215	Pro	vai	vai	ser	220	T
40		1 ::::::	210					213					220	
70	AAO	CTG	TTG	מידי	AAT	CCC	AGT	СТА	CCA	GAA	CAA	CAC	CTA	700
					Asn									, 00
化热点压炉影					225		7,75%	~ <u></u>		230		era era di. Santa di		" DANS
		- 10	: :::		-,				··. · ·		. : ::		17.1.	
45	GTA	ATC	AGA	TCT	GCC	AAT	TTC	ACA	GAC	AAT	GCT	AAA	ACC	739
					Ala									# ./.
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50	Ile	Ile	Val		Leu	Asn	Glu	Thr		Lys	Ile	Asn	Cys	
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	GGA	GAC	ATA	AGA	CAA	GCA	CAT	TGT	AAC	TTA	ACT	ACA	GCA	895
	Glv	Asp	Ile	Aro	Gln	Ala	His	Cvs	Asn	Ile	Ser	Ara	Ala	
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	CAA Gln	TGG Trp 300	AAT Asn	AAG Lys	Thr	TTA Leu	GAA Glu 305	Lys	Val	Val	Asp	Lys 310	Leu	
5	AGA Arg	AAA Lys	CAA Gln	TTT Phe 315	G1 y	GAT Asp	AAT Asn	ACA Thr	ACA Thr 320	ATA Ile	GCT Ala	TTT Phe	AAT Asn	973
10	CGA Arg 325	TCC Ser	TCA Ser	GGA Gly	GLY	GAC Asp 330	CCA Pro	GAA Glu	ATT	GTA Val	ATG Met 335	CAC His	ACT Thr	1012
15	TTT Phe	Asn	TGT Cys 340	GGA Gly	GGG Gly	GAA Glu	TTT Phe	TTC Phe 345	TAC Tyr	TGT	TAA Asn	ACA Thr	ACA Thr 350	1051
. 0:	CAA Gln	CTG Leu	TTT Phe	AAT Asn	AGT: Ser 355	ACT Thr	TGG Trp	AAT Asn	AAT Asn	ACT Thr 360	TGG Trp	AAG Lys	GAT Asp	1090
20	CCT Pro	AAC Asn 365	AGG Arg	AGT Ser	GAC Asp	AAT Asn	ATC 11e 370	ACA Thr	CTC Leu	CCA Pro	TGC Cys	AGA Arg 375	ATA Ile	1129
25	AAA Lys	CAA Gln	ATT	ATA Ile 380	AAC Asn	ATG Met	TGG Trp	CAG Gln	GAA Glu 385	GTA Val	GGA Gly	AAA Lys	GCA Ala	1168
30	ATG Met 390	Tyr	GCC Ala	CCT Pro	CCC	ATC Ile 395	AGA Arg	GGG	GAA Glu	ATT	AGA Arg 400	Cys	TCA Ser	1207
35	TCA Ser	AAT Asn	ATC Ile 405	Thr	GGG Gly	CTG Leu	CTA Leu	CTA Leu 410	Thr	AGA Arg	GAT Asp	GGT Gly	GGT Gly 415	1246
	AAT Asn	GAC Asp	GAT Asp	GGT Gly	AAT Asn 420	Asp	ACG Thr	ACC Thr	ACA Thr	AAC Asn 425	AGG Arg	ACC Thr	GAG Glu	1285
40	ATC Ile	TTC Phe 430	Arg	CCT Pro	GGA Gly	GGA Gly	GGA Gly 435	Asp	ATG Met	AGG Arg	GAC Asp	AAT Asn 440	Trb	1324
45	AGA Arg	AGT Ser	GAA Glu	TTA Leu 445	TAT Tyr	AGA Arg	TAT Tyr	AAA Lys	GTA Val 450	GTA Val	AAA Lys	ATT Ile	GAA Glu	1363
50	CCA Pro 455	Leu	GGA Gly	ATA Ile	Ala	CCC Pro 460	Thr	AGG Arg	GCA Ala	AAG Lys	AGA Arg 465	Arg	GTG Val	1402
55	GTG Val	CAG Glr	AGA Arg 470	G1u	Lys	AGA Arg	Ala	GTA Val 475	Gly	CTA Leu	GGA Gly	Ala	TTG Leu 480	1441
	Phe	CTI Leu	GGG Gly	TTC Phe	TTG Leu 485	Cly	GCA Ala	xaa	AGC	Pne	хаа		:	
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Val Leu 10 Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu 15 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys 20 Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met Thr Asn Cys Ser 25 Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Val Val Pro Ile Glu Glu Asp Asp 30 Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr 3.5 Gln Ala Cys Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys 40 Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Clu Clu Clu Val Val Ile Arg Ser Ala Asn Phe 235 50 Thr Asp Asn Ala Lys Thr Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile 55 Asn Ile Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile Gly Asp Ile Arg Gin Ala His Cys Asn Ile Ser Arg Ala Gin Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu Arg Lys Gln Phe

	Gly Asp	Asn		Thr :	lle	Ala	Phe	Asn	Arg 325	Ser	Ser	Gly	Gly	330
5	Pro Glu	Ile		1et 1	His	Thr	Phe	Asn	Cys 340	Gly	Gly	Glu	Phe	Phe 345
	Tyr Cys	Asn	Thr 1	Thr (	31n	Leu	Phe	Asn	Ser 355	Thr	Trp	Asn	Asn	Thr 360
10	Trp Lys	Asp	Pro /	Asn 1 365	Arg	Ser	Asp	Asn	11e 370	Thr	Leu	Pro	Сув	Arg 375
	Ile Lys	Gln	Ile	lle /	Asn	Met	Trp	Gln	Glu 385	Va1	Gly	Lys	Ala	Met 390
15	Tyr Ala	Pro	Pro	lle 395	Arg	Gly	Glu	Ile	Arg 400	Cys	Ser	Ser	Asn	Ile 405
20	Thr Gly	Leu	Leu !	Leu 410	Thr	Arg	Asp	Gly	Gly 415	Asn	Asp	Asp	Gly	Asn 420
	Asp Thr	Thr	Thr	Asn 425	Arg	Thr	Glu	Ile	Phe 430	Arg	Pro	Gly	Gly	Gly 435
25	Asp Met	Arg	Asp	Asn 440	Trp	Arg	Ser	Glu	Leu 445	Tyr	Arg	Tyr	Lys	Val 450
	Val Lys	Ile	Glu	Pro 455	Leu	Gly	Ile	Alá	Pro 460	Thr	Arg	Ala	Lys	Arg 465
30	Arg Val	Val	Gln	Arg 470	Glu	Lys	Arg	Ala	Val 475	Gly	Leu	Gly	Ala	Leu 480
35	Phe Leu	Gly	Phe	Leu 485	Gly	Ala	Xaa	Ser	Phe 490	Xaa 491	= -	• • • •		
	(2) INFO	TAMGE	ION F	OR S	ro I	T.D. NI	0 - 25 :							
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40	(i) <b>:</b>	SEQUEI (A) LI (B) T (C) S	NCE C ENGTH YPE: TRAND OPOLO	HARA Nucl EDNE	CTE 35 l eic SS: Line	RIST base Aci Sin ear	ICS: pain d gle	s	NO: 2	5:				
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	(XI)  CTC  Let  CTA TT  Leu Ph	SEQUEI (A) LI (B) T (C) S (D) T SEQUE C GAG I Glu I T TGT e Cys	NCE CENGTH YPE: TRAND OPOLO NCE D GTA Val GCA Ala	HARA 1: 14 Nucl EDNE GY: ESCF CCT Pro TCA Ser	CTE 35 h eic SS: Line CIPT GTG Val 5	ACION: TGG Trp GCT Ala	ICS: pain d gle SEQ AAA Lys 20	ID IGAA Glu	GCA Ala TAT Tyr	ACC Thr 10 GAT Asp	TCA Ser	GAG Glu 25	75	
<b>4</b> 5	(i) (i) (ii) (iii)	SEQUEI (A) L(B) T (C) S (C) T SEQUE C GAG C G1U I T TGT C Cys T AAT S ASN	NCE CENGTH YPE: TRAND OPOLO OPOLO GTA Val GCA Ala GTT Val	HARA : 14 Nucl EDNE GY: ESCF CCT Pro TCA Ser TGG Trp 30	CTE 35 l eic SSS: Line Val 5 GAT Asp GCC Ala	ACA Thr	ICS: pain d gle SEQ AAA Lys AAA Lys 20 CAT	ID I GAA Glu GCA Ala	GCA Ala TAT Tyr TGT Cys	ACC Thr 10 GAT Asp GTA Val	TCA Ser CCC Pro	GAG Glu 25 ACA Thr	75 114	l li e
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<b>A</b> 5	(xi) CTA CTA TT Leu Ph GCA CA Ala Hi GAC CC Asp Pr	SEQUEI (A) LI (B) T (C) S (D) T SEQUE C GAG G Glu I TGT E Cys T AAT S AS C AAC O AS O	NCE CENGTH YPE: TRAND OPOLO NCE D GTA Val GCA Ala GTT Val CCA	HARA : 14 Nucl EDNE DGY: CCT Pro TCA Ser TGG Trp 30 CAA Gin ATG Met	CTER 35 ! eicc SS: Linn TRT GTG Val S GAT Asp GCC Ala GAA Glu TCG Trp	RIST Dase Acio Sin Sar ION: TGG Trp GCT Ala ACA Thr GTA Val	ICS: pain d gle SEQ AAA Lys AAA Lys CAT His	ID GAA Glu GCA Ala GCC Ala TTG Leu	GCA Ala TAT Tyr TGT Cys 35 GAA Glu ATC	ACC Thr 10 GAT Asp GTA Val	TCA Ser CCC Pro GTG Val	GAG Glu 25 ACA Thr	75 114 1153	

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	ATG	CAT	GGG	GAT	ATA	ATT	AGT	TTA	TCC	GAT	CAA	AGC	CTA	231
	Met	His	Gly	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	
	65					70			ingr		75			
5	AAG	CCA	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	GTT	ACG	TTA	270
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	ATA	GAG	GGG	GGA	GAA	ATA	AAA	AAT	TGC	TCT	TTC	AAT	ATC	348
	Ile	Glu	Gly	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	
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41 P 34	ACA	GGA	AAC	ATA	ATA	GGA	GAT	ATA	AGA	CAA	GCA	CAT	TGT	855
	Thr	Gly	Asn	Ile	Ile	Gly	Asp	TTE	Arg	Gln	Ala	HIS	285	
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		ATT	хст	CCA	ACA.	AAA	TGG	ΤΛΑ	GAC	ACT	TTG	AAA	AAG	894
5	AAC	Ile	Ser	Glv	Thr	Lvs	Trp	Asn	Asp	Thr	Leu	Lys	Lys	a de la composição de la c
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1. 1.	:. · :						_11			N N W	N D C	A C A	АТА	933
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10	Ile	300	Tre	Lys	Leu	ALG	305			-	- 3 -	310		
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	GTC	TTT	TAA	CAA	TCC	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GCA	9.7.2
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	CCA	TIGO	AGA	ATA	AGA	CAA	ATT	ATA	AAC	ATG	TGG	CAG	AAA	1128
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					 	m n m	CCC	COT	cec	ATC	AAA	GGG	CAA	1167
	ATA	GGA	AAA	GCA	Mot	TOT	Ala	Pro	Pro	Ile	Lys	Gly	Gln	
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		Arg	Cys	Ser	Ser	395	IIe	inr	GIY	Leu	400	. Deu	1112	
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40	AGA	CAT	GGT	GGT	AAC	AAC	AAC	ATG	AGC	AAG	ACC	ACC	GAG	1245
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				CCT	CCA	GGA	GGA	GAT	ATG	AGG	GAC	TAA	TGG	1284
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		7110			420			•		425				
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4.	Pro	Let	ı Gly	v val	Ala	Pro	Thr	Arc	, Ala	Lys	Arc	Arg	yaı	
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		Asn	:: Ile	Ser	Gly	Thr	Lys	Trp	Asn	Asp	Thr	Leu	Lys	Lys	Ile	Ala
						290					295				3	300
		Ile	Lys	Leu	Arg	Glu	Gln	Phe	Asn	Lys	Thr	Ile	Val:	Phe	Asn	Gln :
	5	alaina Ti		• :		305				· i	310			ra Malayir Hara		
		Ser	Ser	Gly	Cly	Asp	Pro	Glu	Ile	Ala	Thr 325	Leu	Ser	Phe	Asn	Cys 330
						320	(11°, 1 d)									
	10	Gly	Gly	Glu	Phe		Tyr	Cys	Asn	Ser	Thr 340	Gln	Leu	Phe	Asn	Ser 345
* *			. ::	•	. # .:	335	Hijt d	· · · · · ·						: " :		
	- 1	Thr	Trp	Asn	Ser	Thr	Gly	Ser	Asn	Asn	Thr 355	Lys	GIA	Asn	Asp	Thr 360
	15					350			34. 					W	muni.	C) n
		Ile	Thr	Leu	Pro	Cys 365	Arg	Ile	Arg	Gln	370	TIE	ASI	me c	TIP	375
			. ()	_ •			i di			Pro	Pró	Tle	Lvs.	Glv	Gln	Ile
	20	Lys	Ile	Gly	rys	380	Met	1 9 1	. VIG		385		x			390
		*			C	A con	Tle	Thr	. 61.v	Leu	Ile	Leu	Thr	Arg	Asp	Gly
•		Arg	Cys	ser	Ser	395	116				400	•				405
	2.5	C1.	, Nen	A e n	Asn	Met	Ser	LVS	Thr	Thr	Glu	Thr	Phe	Arg	Pro	Gly
	25	GIY	Apir	Valle	A5II	410		· <del>-</del> : <b>-</b> : : · · · · ·	)	.1.	415					420
		-c) v	G) v.	A:sp	Met	Arg	Asp	Asn	Trp	Arg	Ser	Glu	Leu	Tyr	Lys	Tyr
		01,	-			425	-X.				430			· . :		435
	30	Lys	Val	val	Lys	Ile	Glu	Pro	Leu	Gly	Val	Ala	Pro	Thr	Arg	Ala 450
						440					443					
		Lys	Arg	Arg	Val	Val	Gln	Arg	Glu	Lys	Arg 460	Ala	Val	Gly	Ile	Gly 465
	35	. : .				455	1 1	". ". 	V		-00	; .	1.11			• • • •
		Ala	Val	Phe	Leu	Gly	Ph∈	Leu	Gly	Ala	Xaa 475	Ser	Phe	Xaa 478		•
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	40	(2)	INFO	RMAT	ION NCE	FOR	SEQ	ID N	10:27 :ICS:	:		5	na Lanca			
1.1			- 1	A) L	ENGT	H: 1	435	base	e par	rs			•			. :
			(	B) T C) S	YPE:	Nuc DEDN	ESS	Sir	ng le	i et g		. :				
	45			D) T	OPOL	OGY:	Li	near	ander er		NO : 2	7		Ar.	· :	
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		, The	CTC	GAG	GTA	CCI	GT(	G TG(	3 AAA D Lve	GAA Glu	GCA	Thr	Thr	Thr	20	
	50		Leu 1			r ( i jir	3.3	5 .	11: p. 7. s	i.	a	10	11			•
		СТА	ттт	TGI	GCA	TCP	GA'	T GC	T AAP	GCA	TAT	GAT	TCA	GAG	75	•
: *		Leu	Phe	Cys	Ala	Ser	As	p Al	a Lys 20	, Ala	Tyr	Ast	Ser	G1u 25		• • •
٠.,:	55			15										707	114	
		GCF	CAT	AA	GTI	TGC	GC Al	C AC a Th	a CAT r His	GCC Ala	Cys	Val	Pro	Thr		
		WIE	HIS	. vai	, 491	3(	)		4.46.		35			. 1		i Notati
	60	GAC	ccc	. AAC	CCA	CA	A GA	A GT	A GA	TTG	GAA	AA I	GTG	ACA	15,3	<b>3</b>
		Asi	Pro	Ası	n Pro	Gli	n Gl	u Va 4	1 GIV	Leu	G1 u	Asr	1 Val	2412		
			40	<i>.</i>	4 - 1	برخني		<b></b>	₹,4;	:	•				0.	1.

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						1115	Wallen.					: ·		
1	GAA	AAT	TTT	AAC	ATG	TGG	AAA	AAT	AAC	ATG	GTA	GAA	CAG	192
	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	:Val	Glu	Gln	
	1 1	. :::::::::::::::::::::::::::::::::::::		. 55		#5. JF	Mile.		60	14.111.11	1 :			
		1.00			. :									
5	ATG	CAT	GGG	GAT	ATA	TTA	AGT	TTA	TGG	GAT	CAA	AGC	CTA	231
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	AAG	CCA	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	GTT	ACG	TTA	270
10								Pro						-8
	-		80		•		1.5	85			•		90	
		.*								٠		•		
	AAT	TGC	ACT	GAC	CCA	AAT	GTT	ACT	AAT:	AGC	GAG	AGA	ACG	309
	Asn	Cys	Thr	Asp	Pro	Asn	Val	Thr	Asn	Ser	Glu	Arg	Thr	
15				-	95	:			1	100		-		
								:	- j.j 1					
	ATA	GAG	GGG	GGA	GAA	ATA	AAA	AAT	TGC	TCT	TTC	AAT	ATC	348
	Ile	Glu	Gly	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	
		105				٠	110			•		.115		
20			٠			· .			7 7 1					
	ACC	ACA	AAC	ATA	AGA	GAT	AGG	TTT	CAG	AAA	GAA	TAT.	GCA	387
	Thr	Thr	Asn	Ile	Arg	Asp	Arg	Phe.	Gln	·Lys	Glu	Tyr	Ala	
		1,3		120	-	:		''	125	:				
			•		. :	:		·· . ·						
25								ATA						426
	Leu	Phe	Tyr	Lys	Leu	Asp	Val	Ile	Pro	Leu	Gly	Asn	Asp	
•	130		:			135					140			
							•	` •	1					
								AGT						465
30	Asn	Thr	Ser	Tyr	Arg	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	
			145					150	.* .				155	
	٠.													
								GTA						504
	Ile	Thr	Gln	Ala		Pro	Lys	Val	ser	Phe	Glu	Pro	Ile	
3.5		:			1.60					165				
							1.7							
	CCC	ATA	CAT	TAT	TGT	GCC	CCG	GCT	GGT	TTT	GCG	ATT	CTA	543
	Pro		His	Tyr	Cys	Ala		Ala	Gly	Phe	Ala		Leú	
	٠.	170					175				. :	180		
40						· ·								
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	Lys	Cys	Lys		Lys	Lys	Phe	Asn	GIY	Thr	Cly	Pro	Cys	- 1. E
			1534	185			1,0		190	1.0				
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45														621
		Asn	Val	Ser	Thr		GIn	Cys	inr	HIS		TIE	Lys.	
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		. C. M.	ስጥ እ	СУТ	מדמ	GGA	CCA	GGC	AGA I	GCA	TTT	TAT	GCA	816
	Lys S	Ser	11	His	TIE	CIA	Pro	Gly	Arg		Phe 270	Tyr	Ala	
	260			''		205						ini iri		
5	ACA C	GA.	AAC	ATA	ATA	GGA	GAT	ATA .	AGA .	CAA	GCA	CAT	TGT	855
	Thr (	Gly	Asn	Ile	Ile	G1y∷	Asp	1 Te	Arg	Gln	Ala	11.20	285	
			2:75	٠.			:11.11.1	ZiPib''						004
	AAC A	TTA	AGT	GGA	ACA	AAA	TGG	AAT	GAC	ACT	TTG	LVS	LVS	894
10	AAC A	Ile	Ser	Gly	7nr 290	Lys	rrp	Mail.	пэр	295				,
***									 	N. R. TT	DDC.	ארט	מדמ	933
	ATA Ile	GCT	ATA	AAA	TTA	AGA	GAA Glu	Gln.	Phe	Asn	Lys	Thr	Ile	,,,,,
15		300	Tie	Lys	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		305					310		
	GTC		N.N.TT	ממי	<b>ייר</b> ר	тса	CGA	GGG	GAC	CCA	GAA	ATT	GCA	972
	Val	TTT Phe	Asn.	Gin	Ser	Ser	Gly	Gly	nob	Pro	Glu	Ile	Ala	ing the second
				315	,				320					* .
20	ACG	CTC	AGT	TTT	AAT	TGT	GGA	GGG	GAA	TTT	TTC	TAC	TGT	1011
	Thr	Leu	Ser	Phe	Asn	Сув	GIY	G1.y	Glu	Phe	335	туг	Cys	
•	325	•				330								.050
25	AAT	TCA	ACA	CAA	CTG	TTT	AAT	AGT	ACT	TGG	AAT	AGT	ACT	1050
	Asn	Ser	Thr 340	Gln	Leu	Phe	Asn	345	4.111	T.P	7.5.		350	
Ť.	•									N.CON	ATIC	ACA	CTC.	1089
	GGG	TCA	AAT	AAC	ACT	AAA Lvs	G1A GGY	AAT	Asp	Thr	Ile	Thr	Leu	1089
30	GIY	Ser	Wall	ASII	355	2,2				360				
			- 14 · .	2002		CNN	<b>ከ</b> ጥጥ	АТА	AAC	ATG	TGG	CAG	AAA	1128
	Pro	Cvs	Ara	Ide	Arg	Gln	Ile	Ile	Asn	Met	Trp	Gln	Lys	e egiligi
35		365					3 //		: :::::					
	מדמ	GGA	AAA	GCA	ATG	TAT	GCC	CCT	ccc	ATC	AAA	GGG	CAA	1167
	Ile	Gly	Lys	Ala	Met	Tyr	Ala	Pro	Pro 385		Lys	GTA	Gin	١.
4.0				380		::,	P. 1	1.77						
4.0	ATT	AGA	TGT	TCA	TCA	AAT	ATT	ACA	GGG	CTA	ATA	TTA	ACA Thr	1206
	Ile	Arg	Cys	Ser	Ser	Asn 395	TTE	Ini	Gry	Leu	400	)		
	390	* *****					·					N.C.C	CAC	1245
4.5	AGA	GAT	GGT	GGT	AAC	AAC	AAC	ATG Met	Ser	Lys	Thr	Thr	Glu	1245
	Arg	Asp	405	GIY	nəi			410			:::::		415	<b>5</b>
						CG2	GGA	GAT	ATG	AGC	GAC	: AAT	TG	1284
50		Phe	AG	Pro	Gly	G13	Gly	Asp	Met	Arc	Ası	) Asr	Tr	<b>)</b>
50					420	)			( _{to} i	425	ya *			
	AGA	AGT	GA	A TT	TAT	IAA 1	TAT	AAA 1	GTA	GT/	AA.	ATT	GA	A 1323
	Arg	Ser	Gl	ı Lei	ı, LAi	Ly	3 TY	Lys	. A GT 1	(Va)				u .
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	GTC	CAC	AG	A GA	A AA	A AG	A GC g Ala	A GTO	. GG/ 1 G1	y 11	e Gl	y Ala	a Va	G 1401 1
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TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435 Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa (2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 478 amino acids (B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

10 Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys 15 Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val 20 Glu Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Clu Gln Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln 25 Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu 30 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Asn Ile 35 Arg Asp Arg Phe Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp Asn Thr Ser Tyr Arg Leu Ile Ser 40 145 Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe 45 Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Thr 50 Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro Val Val Ser Thr Gln Leu Leu Asn Gly Ser Leu Ala Glu Glu Asp fle 55 Val Ile Arg Ser Ala Asn Leu Thr Asp Asn Ala Lys Asn Ile Ile 230 Val Gln Leu Asn Glu Ser Val Thr Met Asn Cys Thr Arg Pro Asn 60

Asn Asn Thr Met Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe

260

65

250

	Tyr Ala Thr Gly Asn Ile Ile Gly Asp Ile Arg Gl 275	n Ala His Cys 285
5	Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Ly 290 295	s Lys Ile Ala 300
	Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile Va 305	
10	Ser Ser Gly Gly Asp Pro Glu Ile Ala Thr Leu Se 320 325	
	Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Le 335	
<b>1</b> 5	Thr Trp Asn Ser Thr Gly Ser Asn Asn Thr Lys Gl	
20	Ile Thr Leu Pro Cys Arg Ile Arg Gln Ile Ile As 365	
	Lys Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Ly 380	
25	Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Th 395	
3.0	Gly Asn Asn Met Ser Lys Thr Thr Glu Thr Pr 410	
30	Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Le 425	
35	Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pr 440. 445.	
	Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Va 455 460	
40	Ala Val Phe Leu Gly Phe Leu Gly Ala Xaa Ser Pl 470 475	he Xaa 478
4.5	(2) INFORMATION FOR SEQ ID NO:29:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 511 amino acids  (B) TYPE: Amino Acid  (D) TOPOLOGY: Linear  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	
5.0	Met Arg Val Lys Gly Ile Arg Arg Asn Tyr Gln H	is Trp Trp Gly Arg
	Gly Thr Met Leu Leu Gly Leu Leu Met Ile Cys S	er Ala Thr Glu Lys 30
55	Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val T	rp Lys Glu Ala Thr 45
60	50	
era dina Markuri fi Markurida	His Asn Val Trp Ala Thr His Ala Cys Val Pro T 65 70 75	hr Asp Pro Asn Pro 80

	1			9.												,,,,,,
	Gln	Glu	Val	Glu	Leu 85	Val	Asn	Val	Thr	Glu 90	Asn	Phe	Asn	Met	Trp 95	Lys
5	Asn	Asn	Met	Val 100	Glu	Gln	Met	His	Glu 105	Asp	Ile	Ile	Ser	Leu 110	Trp	Asn
	Gln	Ser	Leu 115	Lys	Pro	Cys	Val	Lys 120	Leu	Thr	Pro	Leu	Сув 125	Val	Thr	Leu
10	Asn	Cys 130	Thr	Asp	Leu	Arg	Asn 135	Thr	Thr	Asn	Thr	Asn 140		Ser	Thr	Asp
15	Asn 145	Asn	Asn	Ser	Lys	Ser 150	Glu	Gly	Thr	Ile	Lys 155	Gly	Gly	Glu	Met	Lys 160
	Asn	Сув	Ser	Phe	Asn 165	Ile	Thr	Thr	Ser	11e 170	Gly	Asp	Lys	Met	Gln 175	Lys
20	Glu	Tyr	Ala	Leu 180	Leu	Tyr	Lys	Leu	Asp 185	Ile	Glu	Pro	Ile	Asp 190	Asn	Asp
	Ser	Thr	Ser 195	Tyr	Arg	Leu	Ile	Ser 200	Cys	Asn	Thr	Ser	Val 205	Ile	Thr	Gln
25	Ala	Cys 210	Pro	Lys	Ile	Ser	Phe 215	Glu	Pro	Ile	Pro	11e 220	His	Tyr	Cys	Ala
30	Pro 225	Ala	Gly	Phe	Ala	11e 230	Leu	Lys	Cys	Asn	Asp 235	Lys	Lys	Phe	Ser	Gly 240
	*	· · · ·		: .	245	••		• • • •		250				His	255	
35			260					*	265			1.	<del></del>	Leu 270		
			275		٠.			280					285	Ala		il ele Tale
40	1.03	290					295					300				Pro
45	305					310			- 21 (A) 17 (A)		315		we we go	Arg		320
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50				340					345					350		Lys
55			355					360		T.			365	Pro		H
<b>J</b> S		370					375					380		Gly		
60	385					390			` : • . ·		395		87 1511	Trp	·  :,	400
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	Ala Met Tyr Ala Pro Pro Ile Glu Gly Gln Ile Arg Cys Ser 435 440 445	
5	Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Glu Asp Thr 450 455 460	Asp Thi
-1-	Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg 465 470 475	
10	Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu 485 490	Pro Let 495
. •	Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg 500 510	Glu
15		
· .	(2) INFORMATION FOR SEQ ID NO:30 (i) SEQUENCE CHARACTERISTICS:	
20	(A) LENGTH: 2800 base pairs (B) TYPE: Nucleic Acid	1.041)
	(C) STRANDEDNESS: Single (D) TOPOLOGY: Linear	11.
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:	
25	TTCGAGCTCG CCCGACATTG ATTATTGACT AGAGTCGATC GACAGCTGTG	50
	GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC CCAGCAGGCA	100
:	GAAGTATGCA AAGCATGCAT CTCAATTAGT CAGCAACCAG GTGTGGAAAG	150
30	TCCCCAGGCT CCCCAGCAGG CAGAAGTATG CAAAGCATGC ATCTCAATTA	200
	GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG CCCCTAACTC	250
35	CGCCCAGTTC CGCCCATTCT CCGCCCCATG GCTGACTAAT TTTTTTTATT	300
	TATGCAGAGG CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG	350
	AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTA GCTTATCCGG	400
40	CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTCAGGTAA	450
	GTACCGCCTA TAGAGTCTAT AGGCCCACCC CCTTGGCTTC GTTAGAACGC	500
45	GGCTACAATT AATACATAAC CTTTTGGATC GATCCTACTG ACACTGACAT	550
*.	CCACTTTTC TTTTTCTCCA CAGGTGTCCA CTCCCAGGTC CAACTGCACC	600
	TCGCTTCGCG AAGCTAGCTT GGGCTGCATC GATTGAATTC CACTGCCTTC	650
50	CACCAAGCTC TGCAGGATCC CAGAGTCAGG GG TCT GTA TCT TCC TGC Ser Val Ser Ser Cys	697
	지 :	
55		739
:	TGG TGG CTC CAG TTC AGG AAC AGT AAA CCC TGC TCC GAA TAT Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Glu Tyr 10 15	
	TGC CTC TCA CAT CTC GTC AAT CTC CGC GAG GAC TGG GGA CCC	781
60	TGC CTC TCA CAT CTC GTC AAT CTC CGC GAG GAC TGC CGC GAG GAC TGC GAC GAC GAC GAC GAC GAC GAC GAC GAC G	

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	WO 98/01	<b>304</b>													CT/US97/09690	1.:: 1.::
					CAG Gln									ATC Ile	823	
5					GGT Gly										865	* 1
10					GCC Ala										907	
15					CTC Leu 80						Lys			TTG Leu	949	
	GCG	GAT	GCC	ጥርጥ	CTC	AAG	ATG	GCC	GAC			CGA	ጥጥጥ	CCC	991	
2.0					Leu							Arg				
	GGC Gly	AAA Lys	GAC Asp 105	CTT Leu	CCG Pro	GTC Val	CTG Leu	GAC Asp 110	CAG Gln	CTG Leu	CTC Leu	GAG Glu	GTA Val 115	CCT Pro	1033	
25					GCA Ala 120										1075	
30					AAG Lys									ACA Thr 145	1117	
35						Thr								AAA Lys	1159	. :
40					ACA Thr										1201	
45			Glu		ATG Met						Ser			GAT Asp	1243	
		Ser		Lys	CCA Pro				Leu						1285	
50					Thr					Asn				AAT Asn 215	1327	
55					AAA Lys 220									AAC Asn	1369	
60		Ser			ATC Ile		Thr		Ile			Lys		AAA Lys	1411	
65			Ser					Leu			Val.		Ile	GGT Gly		: 2.

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	TAA NBA	AAT Asn	AGT Ser 260	Asn	ACT Thr	ACT Thr	Ser	TAT Tyr 265	Arg	TTG Leu	ATA Ile	AGT Ser	TGT Cys 270	AAC Asn	1495
5	ACC Thr	TCA Ser	GTC Val	ል ጥጥ	ACA Thr	CAA Gln	GCC Ala	TGT Cys	CCA Pro 280	Lys	ACA Thr	TCC Ser	TTT Phe	GAG Glu 285	1537
10	CCA Pro	ATT	CCC Pro	ATA Ile	CAT His 290	Tyr	TGT Cys	GCC Ala	CCG Pro	GCT Ala 295	GGT Gly	TTT Phe	GCG Ala	ATT	1579
15	Leu 300	Lys		Asn	Asp	Asn 305	Lys	Phe	yau	Gly	310	GIA	Pro	Cys	1621
20	Pro	Asn 315	GTC Val	Ser	Thr	Val	G1n 320	Cys	Thr	HIS	GIY	325	Arg	PIO	1663
25	Val	Val	330	Thr	Gln	Leu	Leu	1 Leu 335	Asn :	GIA	ser	Leu	340	GIU	1705
25	AAA Lys	GAG Glu	GTA Val	GTC Val 345	CTT Leu	AGA Arg	TCT Ser	GAA Glu	AAT Asn 350	TTC Phe	ACG Thr	GAC Asp	AAT Asn	GCT Ala 355	1747
30	AAA Lys	ACC Thr	ATA Ile	ATA I.le	GTA Val 360	CAG Gln	CTG Leu	AAC Asn	Glu'	TCT Ser 365	GTA Val	ATA	ATT	GAT Asp	1789
3.5	TGT Cys 370	Met	AGA Arg	CCC Pro	AAC Asn	AAC Asn 375	Asn	ACA Thr	AGA Arg	ACA Thr	AGT Ser 380	TTe	CCT Pro	ATG Met	1831
40	Gly	CCA Pro 385	GGG Gly	AAA Lys	GCA Ala	TTT Phe	TAT Tyr 390	GCA Ala	ACA Thr	GGA Gly	GAT	GTA Val 395	Tie	GGA Gly	1873
	Asp	ATA Ile	AGA Arg 400	Arg	GCA Ala	CAT His	Cya	AAC Asn 405	ATT Ile	AGT Ser	AGA Arg	GCA Ala	GGA Gly 410	TGG Trp	1915
45	AAT	ACC	ACT	TTA Leu 415	Gln	CAG Gln	ATA Ile	GCT Ala	AAA Lys 420	ьys	TTA Leu	AGA Arg	GAA Glu	AAA Lys 425	1957
50	TTT Phe	GAG	Asn	AAA Lys 430	Thr	ATA Ile	GTT Val	TTT Phe	AAT Asn 435	HIS	TCC Ser	TCA Ser	GGA Gly	GGG Gly	1999
5:5	GAC Asp 440	Pro	GAA Glu	ATT	GTA Val	ATG Met 445	His	ACT Thr	TTT	AAT	TGT Cys 450	Gly	GCG	GAA Glu	2041
60	Phe	TTC Phe 455	TGC Cys	TG1 Cys	AAT Asn	TCA Ser	ACA Thr 460	Pro	CTG Leu	TTT Phe	AAT Asn	AGT Ser 465	Thr	TGG	2083
	Asr	. Asp	GCA Ala 470	Gli	Leu	Phe	Asn	AGT Ser 475	Thr	TGG Tru	Asp	Asp	ACT Thr 480	AAA Lys	2125
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5	TGC AGA	ATA AI Ile Ly	AA CAA ys Gln 500	ATT ATA Ile Ile	AAT AT Asn Me	G TGG t Trp 50	Gln	GAA Glu	GTA Val	GGA Gly	2209	
10	AAA GCA Lys Ala 510		yr Ala								2251	
	GAA TCA	AAT AT	TT ACA	GG CTG	CTA TT	A ACA	AGA	GAT	GGT	GGT	2293	
15	Glu Ser 525		le Thr (	3ly Leu 530	Leu Le	u Thr	Arg	Asp 535	Gly	Gly		
20	AAC GAC Asn Asp										2335	
25	GGA GGA Gly Gly	Asn Me				g Ser					2377	
30	TAT AAA Tyr Lys	GTA AT	TA AAA 1 le Lys 570	ATT GAA Ile Glu	CCA TT Pro Le	A GGA u Gly 575	GTA Val	GCA Ala	CCC Pro	ATC Ile 579	2419	
	TAGGCAA	AGA GA	AGAGTGG	r GCAGAG	GAGAA A	AAAGAG	GCAG:	TGAC	ACTA	NGG	2469	
3.5	AGCTATG	TTC CTI	GGGTTC	TGGGA	GCAGC A	GGAAG	CACT	ATGG	GCG	ATA	2519	
	AGCTTTA	ATG CGC	TAGTTT	TCACA	GTTÄA A	TTCGT	AACG	CACT	CAGO	CA	2569	
40	CCGTGTA	TGA AAT	CTAACA	TGCGA	CCTGC A	GAAGC	TTAG	AACC	GAGO	AA	2619	
40	CTTGTTT	ATT GC	AGCTTATA	ATGGT	TACAA A	TAAAC	CAAT	AGCA	TCAC	AĄ.	2669	
	ATTTCAC	AAA TAA	AGCATTI	TTTTC/	ACTGC A	TTCTAC	STTG	TCGT	TTGI	cc.	2719	
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5	Gln	Ile	Ala	Lys 420		Leu	Arg	Glu	Lys 425	Phe	Glu	Asn	Lys	Thr 430	Ile	Val
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10	Asn	Cys 450	Gly	Gly	Glu	Phe	Phe 455	Сув	Cys	Asn	Ser	Thr 460	Pro	Leu	Phe	Asr
15	Ser 465	Thr	Trp	Asn	Asp	Ala 470	Gln	Leu	Phe	Asn	Ser 475	Thr	Trp	Asp	Asp	Thr 480
	Lys	Trp	Ser	Lys	Gly 485	Thr	Asn	G1u	Asn	Asp 490	Thr	Ile	Thr	Leu	His 495	Сув
20	Arg	Ile	Lys	Gln 500	Ile	Ile	Asn	Met	Trp 505	Gln	Glu	Val	Gly	Lys 510	Ala	Met
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30	Thr 545	Glu	Ile	Phe	Arg	Pro 550	Gly	Gly	Gly	Asn	Met 555	Lys	Asp	Asn	Trp	Arg 560
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55	ACT Thr 10	CTA Leu	TTT Phe	TGT Cys	GCA Ala	TCA Ser 15	GAT Asp	GCT Ala	AAA Lys	GCA Ala	TAT Tyr 20	GAT Asp	ACA Thr	GAG Glu	. 2	34.
60								His		TGT Cys						76

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	ccc	AAC Asn	CCA	CAA	GAA	ATA	GGA	TTG	GAA	AAI	Val	Thr	Glu	AAT	
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5	TTT	AAC	ATG	TGG	AAA	AAT	AAC	ATG	GTA.	GAA	CAG	ATG	CAT	GAG	360
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	AGT	ATA	AGA	GAT	AAG	ATG	AAG	TAA	GAA	TAT	GCA	CTT	TTT	TAT	570
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5														GCA Ala 275	990
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15	Leu 290	Ser	Ser	Thr	Lys	Trp 295	Asn	Asn	Thr	Leu	300 200	Gln	Ile	GTT Val	1074
2.0	ACA Thr	AAA Lys 305	TTA Leu	AGA Arg	GAA Glu	CAT	TTT Phe 310	Asn	AAA Lys	ACA Thr	ATA Ile	GTC Val 315	TTT Phe	AAT Asn	1116
25	CAC His	TCC Ser	TCA Ser 320	GGA Gly	GGG Gly	GAC Asp	CCA Pro	GAA Glu 325	ATT	GTA Val	ATG Met	CAC His	AGT Ser 330	TTT Phe	1158
	AAT Asn	TGT Cys	GGA Gly	GGG Gly 335	GAA Glu	TTT Phe	TTC Phe	TAC Tyr	TGT Cys 340	Asn	ACA Thr	ACA Thr	CCA Pro	CTG Leu 345	1200
30								ACT Thr						ACT Thr	1242
35							Gly	AGA Arg				Leu		TGC Cys	1284
40	Arg	ATA Ile 375	AAA Lys	CAA Gln	ATT Ile	ATA Ile	AAC Asn 380	ATG Met	TGG Trp	CAG Gln	GAA Glu	GTA Val 385	GGA Gly	AAA Lys	1326
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50	AAC Asn	AGC Ser	GAA Glu	ACC Thr	GAG Glu 420	ATC Ile	TTC Phe	AGA Arg	CCT Pro	GGA Gly 425	GGA Gly	GGA Gly	GAT Asp	ATG Met	1452
55							Glu	TTA Leu		Lys		Lys		GTA Val	1494
60	AAA Lys	ATT Ile 445	GAA Glu	CCA Pro	TTA Leu	Gly	GTA Val 450	GCA Ala	CCC Pro	ACC Thr	AAG Lys	GCA Ala 455	TAA *		1533

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	Thr	Glu 50	Asn	Phe	Asn	Met	Trp 55	Lys	Asn	Asn	Met	Val 60	Glu	Gln	Met	His
20	Glu 65	Asp	Ilë	Ile	Ser	Leu 70	Trp	Asp	Gln	Ser	Leu 75	Lys	Pro	Cys	Val	Lys 80
2.5	Leu	Thr	Pro	Leu	Cys 85	Val	Thr	Leu	Asn	Cys 90	Thr	Asp	Leu	Lys	Asn 95	Ala
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(2) INFORMATION FOR SEQ ID NO:37:
     (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 36 base pairs
                (B) TYPE: Nucleic Acid
               (C) STRANDEDNESS: Single
                (D) TOPOLOGY: Linear
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
     GGGCGGATCC TCGAGGTACC TGTRTGGAAA GAAGCA 36
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                (D) TOPOLOGY: Linear
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25
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                (B) TYPE: Amino Acid
                (C) STRANDEDNESS: Single
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          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:
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           Ile Gly Pro Gly Arg Ala Phe
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                (C) STRANDEDNESS: Single (D) TOPOLOGY: Linear
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         Leu Gly Pro Gly Ser Thr Phe
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                (B) TYPE: Amino Acid
                (C) STRANDEDNESS: Single
                (D) TOPOLOGY: Linear --
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:
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## WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising an HIV gp120 amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.

- The polypeptide of Claim 1 wherein the polypeptide
   additionally comprises a flag epitope sequence.
  - 3. The polypeptide of Claim 2 wherein the flag epitope sequence is HSV gD-1 flag epitope sequence.

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- 4. The polypeptide of Claim 2 wherein the flag epitope sequence is fused to the HIV gp120 amino acid sequence.
- 20 5. An oligonucleotide of not more than five kilobases encoding an HIV gp120 polypeptide sequence comprising an amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.
- 6. The oligonucleotide of Claim 5 wherein the oligonucleotide includes a nucleotide sequence selected from the group consisting of Sequence ID Nos. 1, 3, 5, 7, 9, 11, 13, 15, 7, 19, 21, 23, 25, and 27, and fragments thereof.
  - 7. The oligonucleotide of Claim 5 wherein the amino acid sequence encoded by the oligonucleotide additionally comprises a flag epitope.

8. The oligonucleotide of Claim 5 wherein the flag epitope is HSV gD-1 flag epitope.

- The oligonucleotide of Claim 7 wherein the flag
   epitope is fused to the HIV gp120 amino acid
   sequence.
- 10. A vaccine comprising gp120 MN and an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof in a suitable carrier.
  - 11. A vaccine comprising:

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- 15 a. a first gp120 polypeptide sequence or a fragment thereof; and
  - b. a breakthrough isolate HIV gp120 polypeptide sequence or a fragment thereof from a vaccinee vaccinated with said first HIV gp120 polypeptide sequence;

wherein said HIV gp120 polypeptide sequences are in a suitable carrier.

- 12. The vaccine of Claim 11 wherein said first HIV
  25 gp120 polypeptide sequence comprises gp120 MN,
  gp120 A244, gp120 MN-GNE6 (Sequence ID No. 31), or
  gp120 MN-GNE8 (Sequence ID No. 33).
- 13. The vaccine of Claim 12 wherein said vaccine
  30 additionally comprises a second gp120 polypeptide
  sequence comprising gp120 MN, gp120 A244, gp120
  MN-GNE6 (Sequence ID No. 31), or gp120 MN-GNE8
  (Sequence ID No. 33), or a fragment thereof,
  wherein said second HIV gp120 polypeptide sequence
  35 is different from said first HIV gp120 polypeptide
  sequence.

14. The vaccine of Claim 13 wherein said first gp120 polypeptide sequence comprises gp120 MN and said second gp120 polypeptide sequence comprises gp120 A244.

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- 15. The vaccine of Claim 14 wherein said breakthrough isolate comprises an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof in a suitable carrier.
- 16. The vaccine of Claim 13 wherein said first gp120 polypeptide sequence comprises gp120 MN and said second gp120 polypeptide sequence comprises gp120 MN-GNE8 (Sequence ID No. 33).
- 17. The vaccine of Claim 16 wherein said breakthrough isolate HIV gp120 polypeptide sequence is an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof, in a suitable carrier.
- 25 18. The vaccine of Claim 13 wherein said breakthrough isolate HIV gp120 polypeptide is from a vaccinee vaccinated with said first and second HIV gp120 polypeptide sequences.

19. A method for making an HIV vaccine comprising adding an HIV gp120 polypeptide sequence or fragments thereof from a breakthrough isolate from a vaccinee to the vaccine with which the vaccinee was vaccinated.

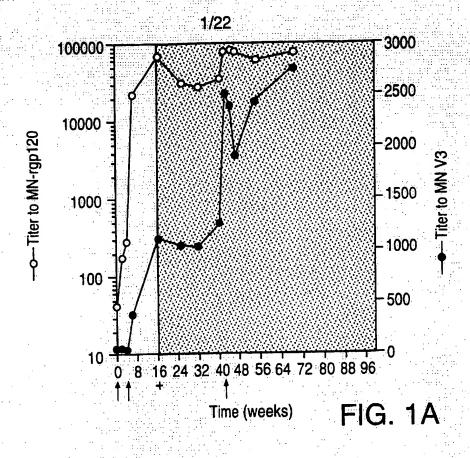
- 20. The vaccine of Claim 11 wherein said first gp120 polypeptide sequence is from a macrophage-tropic HIV-1 strain.
- 21. The vaccine of Claim 11 wherein said first gp120 polypeptide sequence is from a T-cell-tropic HIV-1

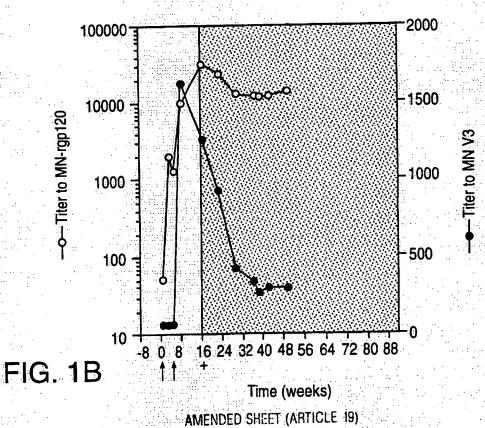
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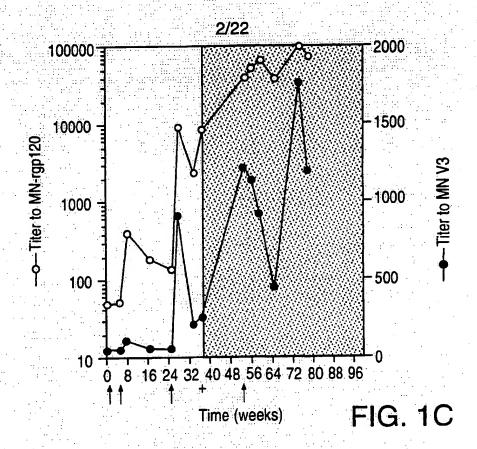
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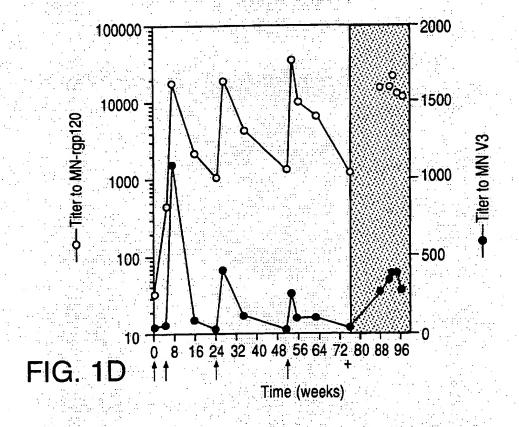
strain.

- 15 22. The vaccine of Claim 21 wherein said vaccine additionally comprises a second gp120 polypeptide sequence or a fragment, from a macrophage-tropic HIV-1 strain.
- 20 23. The vaccine of Claim 22 wherein said first and second gp120 polypeptide sequences bind to different chemokine receptors.
- 24. The vaccine of Claim 23 wherein said first gp120 polypeptide sequence binds to CC-CKR-5 and said second gp 120 polypeptide sequence binds to CXC-CKR-4.
- 25. The vaccine of Claim 11 wherein said vaccine additionally comprises an virus engineered to induce a cytotoxic T-cell response.



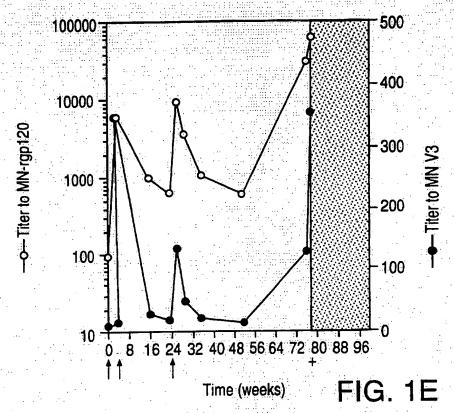


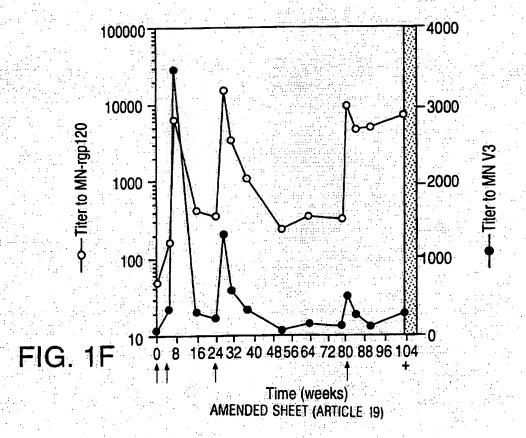




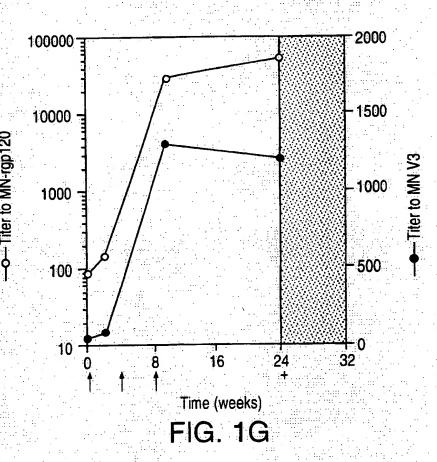


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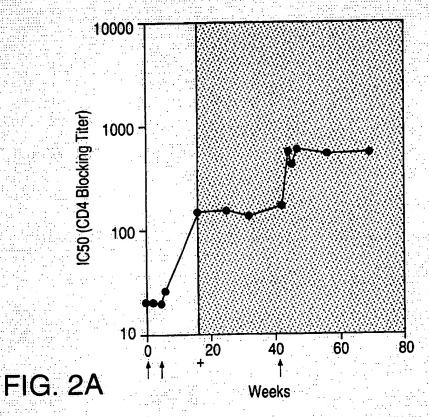


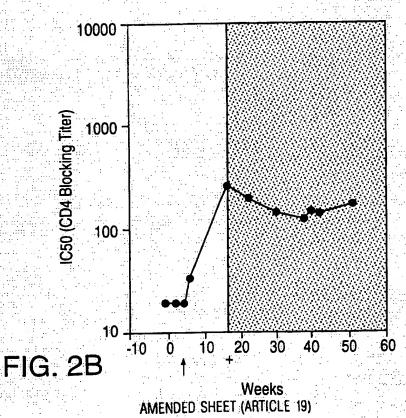


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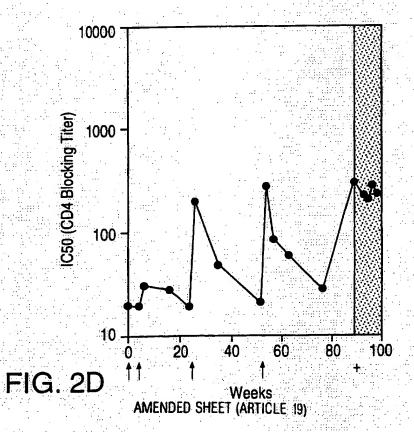




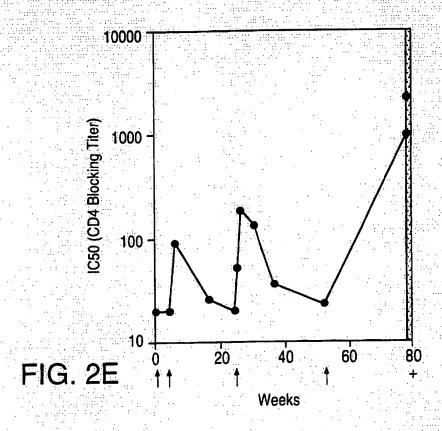


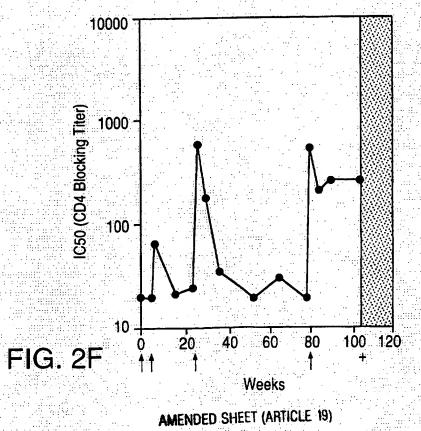


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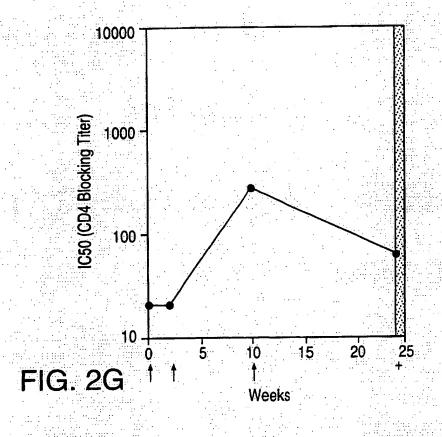


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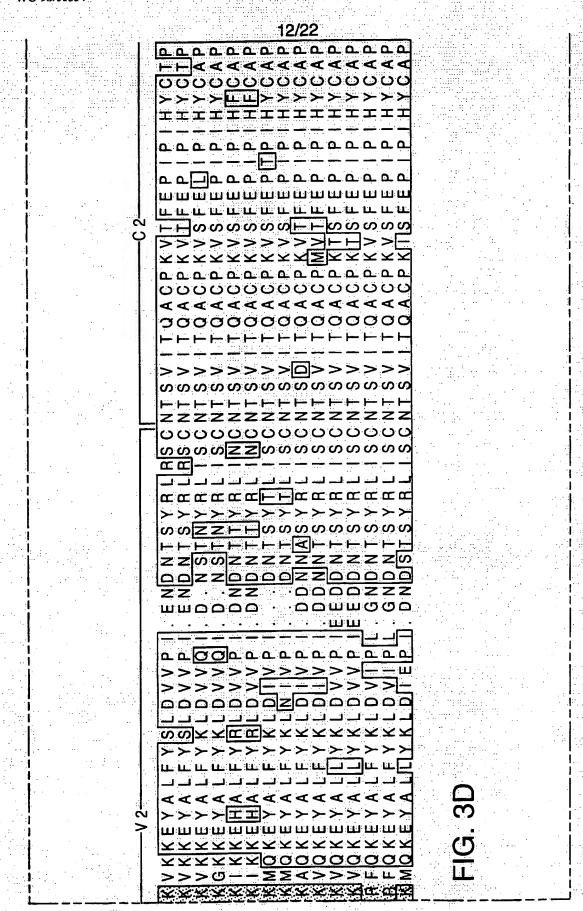
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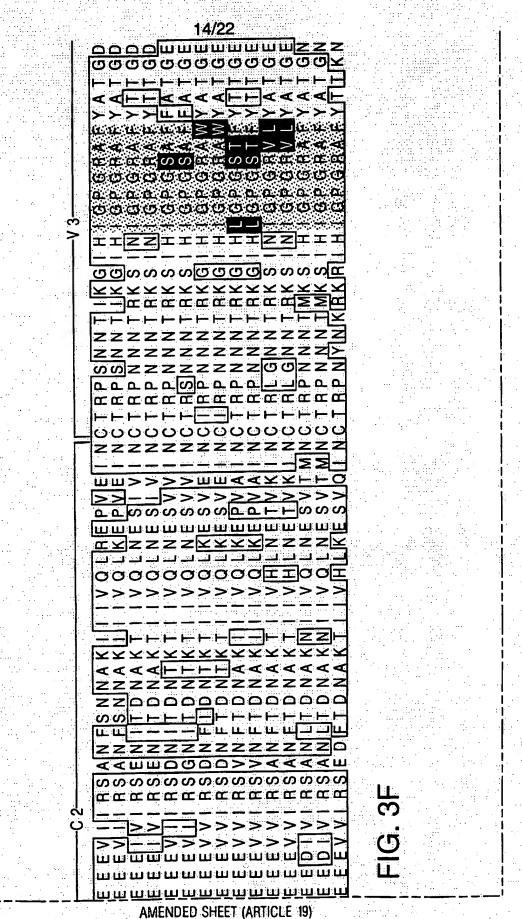
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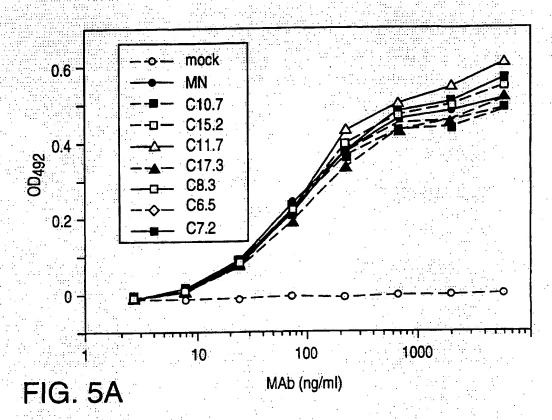
8) B

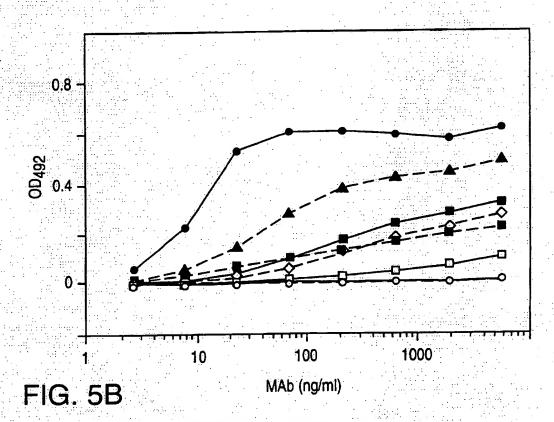


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AMENDED SHEET (ARTICLE 19)

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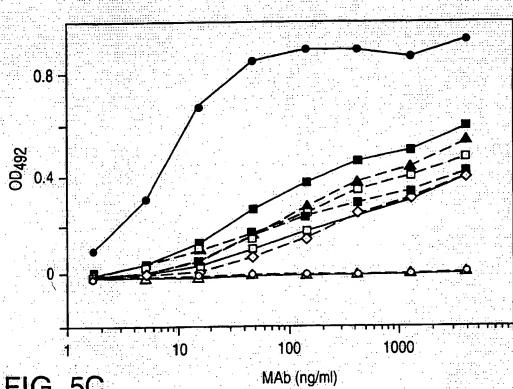


FIG. 5C

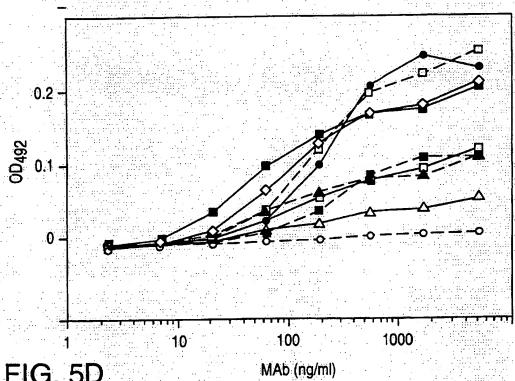


FIG. 5D

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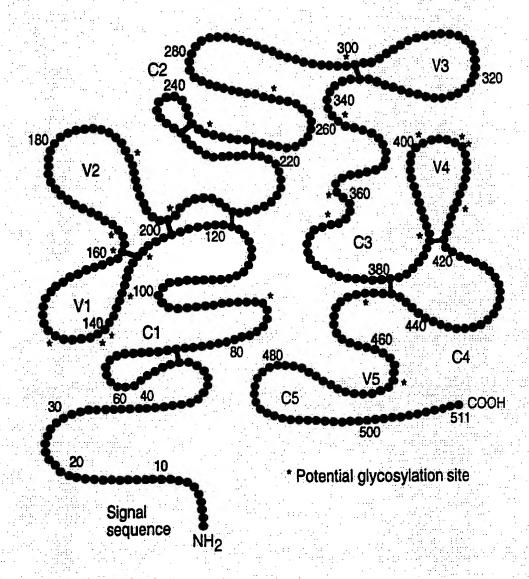


FIG. 6

## INTERNATIONAL SEARCH REPORT

Interr nal Application No PCT/US 97/09690

A CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/49 C07 C07K14/16 A61K39/21 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols): IPC 6 C12N C07K A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages 1-18, WO 94 28929 A (GENETECH, INC.) 22 December X 20-25 see page 56 SEQ. ID. NO. 25. see page 50, line 14 - line 31 1.5.6 P.W. BERMAN ET AL.: "Genetic and X immunologic characterization of viruses infecting MN-rgp120 vaccinated volunteers" ONE WORLD, ONE HOPE: XI INTERNATIONAL CONFERENCE ON AIDS, vol. 10, no. supplement 3, 7 - 12 July 1996, VANCOUVER, CANADA, page 10 XP002045307 See "Methods" in Abstract Mo.A.285 Patent family members are listed in annex Further documents are listed in the continuation of box C. cial categories of cited documents : later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the *A*. document defining the general state of the art which is not considered to be of particular relevance "X" document of perticular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone earlier document but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as especified) document of particular relevance; the claimed invention cannot be considered to involve an inventive stap when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. document referring to an oral disclosure, use, exhibition or document published prior to the international filing date but later than the priority date claimed "&". document member of the same patent family. Date of mailing of the international search report Date of the actual completion of the international search **26 -11- 1997** 30 October 1997 Authorized office: Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016 Cupido, M

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## INTERNATIONAL SEARCH REPORT

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	ition) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
À	M.J. MCELRATH ET AL.: "Human immunodeficiency virus type 1 infection despite prior immunization with a recombinant envelope vaccine regimen" PROCEEDINGS OF THE NATIONAL ACADEMY OF	19
-	SCIENCES OF USA, vol. 93, no. 9, 30 April 1996, WASHINGTON US, pages 3972-3977, XP002045308	
	see page 3976, last paragraph; figure 1	
Т	P.W. BERMAN ET AL.: "Genetic and immunologic characterization of viruses infecting MN-rgp120-vaccinated volunteers	1-25
~	THE JOURNAL OF INFECTIOUS DISEASES, vol. 176, no. 2, August 1997, pages 384-397, XP002045309	
	see the whole document	
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## INTERNATIONAL SEARCH REPORT

information on patent family members

Inter inal Application No.
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